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OSTEOCHONDRITIS DISSECANS

A RÉSUMÉ OF THE THEORIES OF ETIOLOGY AND THE CONSIDERATION OF HEREDITY AS AN ETIOLOGIC FACTOR *

GEORGE WAGONER, M.D.

AND

BERNARD N. E. COHN, A.B.

PHILADELPHIA

Osteochondritis dissecans is a noninfectious process involving the articular cartilage and the subchondral bone of certain long bones of the extremities, which, by sequestration from the articular surface, usually produces a single foreign body or, more rarely, two, in the contiguous joint. This body is originally of an osseocartilaginous composition, but its structure subsequently undergoes alteration by the fluids in the joints. The mesial half of the articular surface of the internal femoral condyle is the site most frequently involved, but the heads of the radius, femur and humerus may also be the sites of the process. Osteochondritis dissecans occurs preeminently in youth, and most commonly in the tall, rapidly growing boy.

OTHER TYPES OF BODIES OF THE JOINTS

Free bodies within the joints are encountered in conditions other than osteochondritis dissecans. All such bodies are grouped under the common heading of corpora libera articularum or "joint mice."

1. Free bodies of traumatic origin may arise in otherwise normal joints. Cartilaginous or bony "mice" occasionally follow severe trauma to the bones comprising a joint. Pieces of normal cartilage or bone may be torn loose and appear free within the joint. An example is found in fractures of the semilunar cartilages. Severe traumas to the joints are frequently followed by the periarticular formation of bone.

2. Free bodies may appear in joints that are the site of arthritis deformans. These bodies arise by the traumatic or necrotic freeing of articular cartilaginous plaques, hypertrophic bony spurs, bony joint papillae, metaplastic cartilage or hypertrophic fibrinous synovial villi. These bodies usually are present in large numbers, vary greatly in size and frequently present a mulberry-like surface.

3. The polypoid bodies present in the hypertrophic type of arthropathic tabétique (incorrectly known as Charcot's joint) present the same

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* From the Department of Pathology, School of Medicine, and the Department of Orthopaedic Surgery, Graduate School of Medicine, University of Pennsylvania.

general etiology noted for free bodies appearing in the joints in arthritis deformans.

4. Masses of uric acid salts, usually sodium biurate, of various sizes are frequently found free within gouty joints.

5. Osteomyelitic sequestrums occasionally appear within a joint.

6. Parts of tumors of the capsule in chondromatosis of a joint sometimes are found free within the joint.

7. Fibrous or lipomatous joint papillae (*lipoma arborescens*) occasionally become loosened and form free bodies in the joints.

8. Parts of hypertrophic synovial villi following a synovitis may be severed from their base by trauma or necrosis and appear within the joint as free bodies. When these villi or papillae contain cartilaginous foci or "rests," the process becomes known as "synovitis prolifera cartilaginea."

9. Corpora oryzoidea (rice bodies) arise as a result of tuberculous involvement of the structures adjacent to a joint. They are numerous, and their structures are those of fibrinoid lamellated masses.

10. Following hemorrhage into, or inflammation of, a joint, masses of fibrin may result and lay free within the joint.

11. Foreign bodies from external sources may become lodged within the joint.

THEORIES OF ETIOLOGY

A careful study of the literature of osteochondritis dissecans discloses many theories of etiology. This literature is grouped into two large divisions: (1) papers in which trauma is set forth as the chief etiologic factor and (2) papers in which factors other than trauma are advanced as causative agents.

The papers emphasizing trauma as the cause of osteochondritis dissecans will be presented first; the various other theories of etiology will then be considered in chronological order.

The first description of loose bodies in joints was made by Pechlin, about 250 years ago.

Trauma as a Causative Agent in Osteochondritis Dissecans.—Monro (1726) advanced the theory that loose bodies within the joints were of traumatic origin. In this belief he was supported by Riemar (1770) and by Haller (1776).

In 1848, Rainey "observed that fragments of cartilage and bone detached within the joint by trauma continued to grow and become sizable loose bodies."

That the production of joint mice arose only through trauma or arthritis deformans was contended by Brodhurst, in 1861, and was upheld by Poncet, in 1881.

Kragelund (1884) assumed a trauma of the "bone-cartilage region," followed by the demarcation and separation of a portion of this area by a chronic inflammatory process. In 1887, this author, experimenting on the knees of cadavers, corroborated the opinion of Paget by finding it "impossible to detach a fragment of articular cartilage simply by a blow; an area was loosened in this manner, but in order to separate it, a prying force had to be applied." Burghard (1892) produced a complete separation of a piece of articular cartilage by an oblique blow on the internal condyle when the knee was flexed.

Conflicting results were obtained by Hildebrand (1896), who found it impossible to produce permanent free bodies in the joints of animals by the surgical detachment of fragments of either cartilage or cartilage and bone.

Preiser (1898) considered osteochondritis dissecans to be the result of static imperfection. Harris (1901) found that "in my subsequent study of these cases there is almost no one who reports a case who does not reach the conclusion that König was wrong."

Boerner (1903) insisted "upon a purely mechanical basis" for the origin of these bodies. Codman (1903), from experimental work on cadavers, concluded that "the life history of the loose cartilage must comprise two injuries, one to depress it, and one to free it."

Cornil and Coudray (1905) found that bodies of traumatic origin produced through experiment in animals became united to the articular extremity of the bone or to the synovial membrane of the joint.

Rimann (1905), following experiments on both dogs and goats, stated, "there is neither a secondary nor a primary osteochondritis dissecans. True, free joint bodies arise only upon a traumatic basis."

Ludloff (1908) advanced the following theory:

The loose bodies arising from the lateral surface of the mesial condyle result from injury to the *arteria genu media* at the point where it perforates the posterior capsule of the joint, and before it enters the bone at the seat of insertion of the posterior crucial ligament. The resulting circulatory disturbance leads to necrosis of the area of bone supplied by the injured vessel. The necrotic bone is gradually separated as the result of insufficient nutrition.

Axhausen (1914) indicated that the vascular system might play a slightly different rôle than that expressed by Ludloff. He assumed:

As the result of the impaction from the opposing articular surface, the blood vessels to the part are damaged, either with or without partial fracture, according to the severity of the violence. This leads to necrosis of the area supplied by the damaged vessels. Instead of creeping substitution of the necrotic bone or bone and overlying cartilage, as would result in case of aseptic bone necrosis in other regions, there forms a zone of absorption resulting in gradual separation and eventual extrusion of the dead portion of the joint.

Friedrich (1913), Bernard (1925), Brackett and Hall (1927) and Schumm (1928) all favored the theory of traumatism.

Fisher (1920) stated:

Not infrequent detachment by indirect injury is produced by violent tension upon the posterior ligament of the knee joint, which is attached immediately adjacent to the articular margin and is powerfully reinforced by the tendons of the gastrocnemius and semimembranosus.

To strengthen his argument in regard to the factor of trauma, Fisher chiseled off a small piece of articular cartilage together with a portion of the underlying bone from the femoral condyle of a rabbit. "The portion was completely detached and pushed up into the supra-patellar recess of the joint," which was then closed. Five weeks later, the loose body was removed. On microscopic examination he found the following changes:

The majority of cartilage cells are perfectly healthy but many of the bone corpuscles are dead. The latter must have died after detachment, therefore it seems reasonable to assume that the bone corpuscles in the classical type of loose body have also died after the detachment by trauma, and that their death is not due to any morbid pathological process. This fact cannot therefore be adduced in favor of some pathological process such as "quiet necrosis."

Kappis (1920) pointed out that in the knee and the elbow, which are the common seats of loose bodies, tangential and rotating forces may act on the convex surface of the condyle and fissure or partially or completely detach portions of the articular end. He thinks that loose bodies arising from the patella are the result of tangential forces. To explain the traumatic origin in the absence of serious injury, he assumed a predisposition as the result of disease or congenital disturbance of the articular cartilage. "Articular cartilage has no nerve supply and the underlying spongy bone is extremely insensitive. This should permit of the occurrence of fracture with little or no serious injury."

Phemister (1920) believed "that osteochondritis dissecans in all cases is a fracture caused by mechanical relationships or slight, unnoticeable trauma which results in either complete or partial separation of the piece in question."

Hellström (1922) assumed:

The joint mice in osteochondritis dissecans are the result of a subchondral impression fracture. Excessive effort due to special structural conditions of the knee joint may lead to the production of these fractures. Hence, individual predisposition plays a part in the development. The failure of firm healing of the fracture completes the clinical picture. There is no spontaneous dissecting osteochondritis in König's sense, and therefore it is best to give up the idea entirely. In giving a legal opinion on the so-called dissecting osteochondritis, the condition must be regarded as an occupational disease produced by trauma.

Freiberg (1923), by a roengenographic study of five cases and the knees of a number of cadavers, found the following:

It was quite easy, even where the tubercle was not long, to make it impinge upon the posterior crucial ligament when the knee was flexed and the tibia rotated outwards. Where the tubercle is long the impingement occurs much sooner, and it seems easily conceivable that it might take place with enough force to damage a small vessel were this to be found just in the right place. For the present, at least, it would seem as if we must look upon this interesting condition as the result of trauma.

Sommer (1923) reported:

The exciting cause akin to necrosis of the cartilage in animal experiments, is contusion that does not lead to death of the cartilage, but introduces the process of dissection and separates the contused tissue from the healthy portions of the joint by aseptic dissection.

Burckhardt (1923) claimed:

The chief reason for many misunderstandings on this question lies in the fact that so far we have been unable to form any satisfactory idea of the nature of the mechanical forces on which it is based, so that it is not known whether the traumas reported in the histories are sufficient in force to produce a fracture from pressure or from bursting.

Burckhardt experimented on cadavers and showed that injury of the median condyle takes place from pressure of the patella. In an incipient case the patella, as a result of fixation by the quadriceps, was pushed with great force against the underlying structures. The amount of this force was calculated according to the laws of mechanics, and it was shown that sufficient force could be derived from contraction of the quadriceps extensor muscle to produce a fracture. That a trauma with such force should cause as little pain as is generally reported is explained by the absence of sensory fibers in the cartilage of the joint. The question of the etiology of joint mice is, therefore, only a problem of the mechanics, of joints and muscles and the histologic pictures are the expression of a reaction of the tissues to a trauma under certain mechanical and anatomic conditions.

Schmidt (1924) demonstrated on the cadaver that at the level of the condyles the cartilage in a joint was more easily injured by a tangential than by a vertical force. He further ascertained the varying positions of the patella when the leg was internally and externally rotated from a position of 60 degrees flexion. He found that when the leg is rotated outward the patella comes in contact with the external condyle; when it is rotated inward, it comes in contact with the internal condyle. In this gliding from one condyle to the other, the tip of the patella moves through a greater arc than does the base. With the leg flexed at 90 degrees or more, the upper border of the patella lies above the condyles.

Schmidt claimed that condylar fragments are broken off by impact between the patella and the condyles following sudden rotations of the leg when in flexion.

According to Phemister (1924) :

In many instances there is a history of traumas with impaction, either alone or combined with rotation or hinge motion in the joint. . . . In dogs, pieces of bone and cartilage chipped off and reinserted in their beds, become reattached in practically every instance. They are usually absorbed and disappear completely in a few months.

The same author was unable experimentally to produce loose bodies within joints by creating necrotic areas in the articular cartilage or subchondral bone by the insertion of radium needle.

Timbrell Fisher (1924) pointed out :

Trauma to the epiphysis will produce a low grade type of inflammatory process in a certain area which thus has lowered vitality, and which may be gradually exfoliated.

Häuptli (1924) stated :

Osteochondritis dissecans is a purely traumatic, complete or incomplete detachment of cartilage or bone-cartilage bodies in the knee or elbow. If bits are incompletely broken off, the processes of healing in the fragments lead to a rudimentary callous formation and now and then to consolidation. The frequent traumas of daily life with the physiologic movements of the knee bring about entire separation of the detached bodies. A necessary predisposition to the disease is created, on the one hand, by a special bone configuration in the joint, and on the other hand, by hypothyroidism (hyperthyroidism?) and late rickets, but most of all by an arthritic constitution.

Leb (1924) disagreed with the authors who believe the following to be true :

A chronic inflammatory process must be declined as the fundamental cause of the illness in default of actual proof. No proof has been produced for the so-called osteochondritis dissecans as an independent, chronic inflammatory procedure. Its symptom-complex could indeed be kept within the bounds of the form of illness of arthritis deformans, of the specific inflammatory process in bone, not, however, separated from every form of traumatic joint mouse formation. The harmony of the clinical and roentgenological pictures as well as the "anamnese" does not exclude the traumatic damage in the course of the daily work, and forces one to the assumption that the illness described as osteochondritis dissecans is subordinated to the domain of joint fractures.

Von Dittrich (1925) thought "that osteochondritis dissecans is the result of mechanical and functional traumatic influence."

Balensweig (1925) believed that osteochondritis dissecans was the result of "an osteochondral fracture of the external femoral condyle as a result of cross strain, aided by the pull of the anterior crucial ligament."

Wolbach and Allison (1928) offered an explanation of its etiology:

The separation was the effect of mechanical pressure on a portion of the articular cartilage with underlying cancellous bone bridging a "cyst." This pressure probably was intermittent as occasioned by variation in functional performances of the joint, and probably was the result of stresses operating roughly in the long axis of the bone and laterally in the anterior-posterior direction. . . . There are two essentials to our explanation; one, a sufficient loss in the condyle of cancellous bone to weaken materially the support of the articular cartilage as a whole; the other, the presence of a "cyst" immediately below the articular cartilage in a position subject to vertical and horizontal stresses. The rarity of typical instances of osteochondritis dissecans of the femur suggests that our observation, even if dependent on the fortuitous existence and distribution of "cysts," may apply to other examples.

Richards (1928), in describing the roentgenologic picture of osteochondritis dissecans, wrote:

In one of our cases the lesion was found in both knees of the individual, and in both of these, the mesial tubercle of the tibial spine was elongated, thus suggesting a purely local process due to this peculiarity.

Causative Agents Other than Trauma in Osteochondritis Dissecans.—Many investigators do not consider trauma the causative agent in osteochondritis dissecans.

John Hunter (1793) believed that the formation of cartilaginous bodies in joints was due to extravasated blood which assumed the nature of the parts into which it was effused.

Rokitansky (1851) stated that "bodies composed of bone and cartilage might arise from the articular serosa, representing an excessive development and ossification of isolated nodules of cartilage." Laennec (1854) indicated that an arthritis was the basis, while Broca (1854) assumed a dry sequestration process as the cause of loose bodies in joints.

Klein (1864) disagreed with these modes of origin. It is "most likely a question of a spontaneous demarcation of part of the joint of the femur."

Paget (1870) could not conceive how pieces of articular cartilage could be detached from living bone by trauma; ". . . these loose bodies are sequestra, exfoliated after necrosis of injured portions of cartilage, exfoliated without acute inflammation."

Koch (1879), performing experiments on embolic necrosis of the bone, proved to his own satisfaction that loose bodies were the result of "the obstruction of the entire capillary area of nutrition."

Poulet and Vaillard (1885) believed that osteocartilaginous bodies were due to "a spontaneous necrosis and a secondary loosening."

In 1887, König published his article, "Ueber freie Körper in den Gelenken," in which he described one type of loose bodies within joints: after his clinical and anatomic studies of these he felt justified in segre-

gating them into a pathologic entity which he termed osteochondritis dissecans. He pointed out that this condition may occur in any joint, but that it most frequently involves the knee and elbow joints in young persons. He was unable to elicit a definite history of trauma in any of his cases, and having excluded arthritis deformans, acute and chronic suppurative or tuberculous osteomyelitis and tabes as the cause of the loose bodies, he concluded that it was a question of a "blasting" of a piece of the surface of the joint by a "dissecting osteochondritis," which resulted in the "severance of a piece of the joint surface without otherwise noteworthy damage to the joint itself." He did not deny that trauma may be a factor in the production of "corpus mobile," but only so far as it gives rise to the "occasion of bringing into prominence the complaints of a joint body which had already existed for a long time." He admitted, however, that "the etiology of this pathological-anatomical process remains obscure." The appearance of König's article occasioned much controversy.

Humphrey (1888) was skeptical about trauma as an etiologic factor, as it would require "a very extraordinary and violent accident that would break off into the knee joint a piece of articular cartilage." He cited as the etiology, descriptions of pathologic processes now established as those associated with arthritis.

Halstead (1895) was inclined to agree with König "that few, if any" of the loose bodies found in otherwise normal joints "are the direct result of violence."

Barth (1896) considered that proof for the existence of osteochondritis dissecans as an entity was lacking, and that König's clinical and operative observations were of doubtful value. He claimed that only by trauma and arthritis deformans could loose bodies arise in joints. Barth excluded a necrotic process as a causative agent by demonstrating living cartilage in free bodies within joints. However, he failed to consider that bodies within joints could receive nutriment from the synovial fluid. Lindenstein (1906) and Brehm (1913) reported cases which they believed corroborated Barth's opinion.

Freiberg and Wooley (1910), reporting a doubtful case of osteochondritis dissecans, agreed with Wollenberg's theory of vascular changes secondary to arthritis deformans as being the cause of free bodies within joints.

Weil (1912) reported two cases of bilateral symmetrical osteochondritis dissecans. He considered Ludloff's theory of inflammatory foci the explanation for the bilateral symmetry of the lesions.

Colvin (1920) believed the process to be infectious, while Reiger (1920) considered it one of infarction secondary to a fat embolus.

Buchner and Rieger (1921), in order to disprove the traumatic theory, showed that 184.3 Kg. of force was necessary for the loosening

ing of a piece from the femoral condyle by extension of the crucial ligament and 614 Kg. by pressure of the patella against the femoral condyle.

Nussbaum (1923), after studying the possibility of the embolic origin of free bodies in the knee joint, came to the conclusion that such a theory was not tenable, as the *arteria genu media* was not an end artery. Axhausen (1924) disputed Nussbaum's conclusions:

The theory of the embolic origin of joint bodies rests on three pillars: (1) mycotic-embolic closure of an epiphyseal artery may lead rapidly to epiphyseal necrosis. (2) The bacteria deposited may be vanquished by the body so that an infection does not take place and the necrosis remains aseptic. (3) Joint bodies may develop in situ from the aseptic epiphyseal necrosis by a process of demarcation. Nussbaum's statements are concerned exclusively with the first and third possibilities. On account of the extent of his examinations, his judgment must be regarded as especially valuable on the question of whether an epiphyseal necrosis may develop from embolic occlusion of a vessel. But it is highly noteworthy that he has a tendency to answer this question in the affirmative for the lower end of the femur. To be sure the epiphyseal arteries are not terminal arteries in an anatomic sense, as fine lateral connections can be demonstrated. But these anatomic findings do not prove that the functional capacity of the fine connections is sufficient to ensure the nutrition of the epiphyseal region on closure of the chief artery. Observations in osseous tuberculosis seem to prove that the lateral connections do not suffice for this, and that therefore, the epiphyseal arteries are "functional" end arteries, and if they are occluded there must be an interruption of nutrition in the area they supply. The tuberculous wedge-shaped necrosis in the lower epiphysis of the femur, with its apex directed toward the diaphysis, may very well correspond to a single epiphyseal vessel area. Nussbaum's admission that the cone shaped sequestrum of the epiphysis may be brought about even without end arteries in the anatomic sense, is a valuable support for the first theory; it does not argue against but in favor of, an embolic genesis. His evidence against an embolic origin is directed solely against the third theory. The point of embolic vessel occlusion is not at a site of separation but much higher up, probably at the same place where Nussbaum assumes occlusion in tuberculous embolic wedge shaped necrosis. The theory of the embolic origin of joint bodies cannot be regarded as shaken or even answered by Nussbaum's anatomic examinations. On the contrary, they give the theory a certain support, as they confirm the possibility of the development of epiphyseal wedge shaped necrosis by the embolic route.

In further consideration of the rôle of the vascular system, Axhausen (1924) stated that the primary lesion is a necrosis of the epiphysis. This is followed by a proliferation of the surrounding tissues that penetrate into the dead bone, and may end with complete reorganization. This regeneration is interrupted by a compression fracture of the diseased epiphysis, which is frequently erroneously considered as the beginning of the disease. The fracture is limited everywhere by dead tissue, and therefore healing is impossible. The ends rub against each other and produce "bone flour." Instead of a comparatively quick substitution, a slow resorption sets in. The cartilage is not yet severely changed, but the necrotic part of the epiphysis

begins to be demarcated from the remaining bone by a layer of granulations or of older connective tissue. A slight injury may free the necrotic part in the elbow or knee joint, because these are broad and especially exposed to such injuries. As to the primary cause of the necrosis, he admits the possibility of torsion of blood vessels, especially in dislocations, but believes that benign infected emboli are more probable. In 1925, this author concluded that "the cause of the epiphyseal necrosis, which is the basis of all these joint diseases, is not yet proven. However, according to new investigations, I maintain their explanation as bland mycotic embolic necrosis." Lehmann (1925) did not agree entirely with Axhausen. "The theory of Axhausen, that a pathological fracture lies at the bottom of osteochondritis dissecans, is the most plausible; on the other hand, the assumption of a bland, necrotic embolus has been rejected because every provable case is without it." According to Walter (1926), "the König-Axhausen theory of emboli as the cause of subchondral bone necrosis experiences a corroboration through such cases in which multiple necrosis appears in reference to 'Infektionskrankheiten'." Besides a bilateral osteochondritis dissecans of both knee joints in a man, aged 22, he found a typical foci in the capitulum radii.

Konjetzny (1924) found an obvious endarteritis obliterans. "Perivascular round cell infiltration which was found here and there, may be thought of as an inflammatory origin."

According to Kroh, Lieck is of the opinion that the condition is due to "Hormonale Störung der inneren Sekretion."

Bernstein (1925) suggested:

There must be some underlying constitutional factor, probably a congenital predisposition of the joint tissues, which is indispensable in the formation of loose bodies in the knee joint. It would also account for the occurrence of loose bodies in homologous joints in the same patient. Granting the existence of such an hereditary predisposition, any exciting causes, such as traumatism, inflammatory changes would act as an exciting cause for the formation of loose bodies in such a joint.

Heine (1927) accepted Axhausen's theory as being, "theoretically at least, the most likely hypothesis," and at the same time rejected Rieger's theory of an arterial fat embolus as "not only an improbable but an impossible hypothesis."

Moulouguet (1929) considered:

A very definite relation between the dry arthritis and the osteochondritis dissecans; in the exfoliation of the cartilage, the partial necrosis of the epiphysis may be the lesions of dry arthritis which, in miniature, produce the process of osteochondritis dissecans.

REPORT OF CASES

CASE 1.—*History*.—C. H.,¹ a tall, white boy, aged 15, was first seen in the outpatient department on May 10, 1928. He complained of limitation of motion of the joint of the left knee. For the past four years the patient had had intermittent disability of the left knee joint. This disability consisted of slight limitation of motion, occasional pain and infrequent "locking" of the knee joint. The "locking" was accompanied by the slight swelling of the soft parts on the inner side of the joint. The patient was always able to "unlock" the knee without



Fig. 1 (case 1).—Left knee joint; the loosened osteocartilaginous body is shown on the mesial aspect of the internal femoral condyle.

assistance. No history of trauma could be obtained to account for the original attack. One week previous to admission, the patient was kicked above the left knee. The part became swollen and painful; the patient was unable fully to extend the leg or to flex it beyond a right angle.

Examination.—The patient walked with a limp of the left lower extremity. Flexion stopped at 90 and extension at 165 degrees. Swelling and induration about

1. From the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases, surgical service of Dr. William J. Taylor.

the knee were absent. A point of tenderness was demonstrated at the anterior margin of the tibial attachment of the left internal lateral ligament.

A diagnosis of osteochondritis dissecans was made and confirmed by a roentgenogram (fig. 1).

Treatment.—Normal motion was restored to the knee joint by a course of baking and massage.

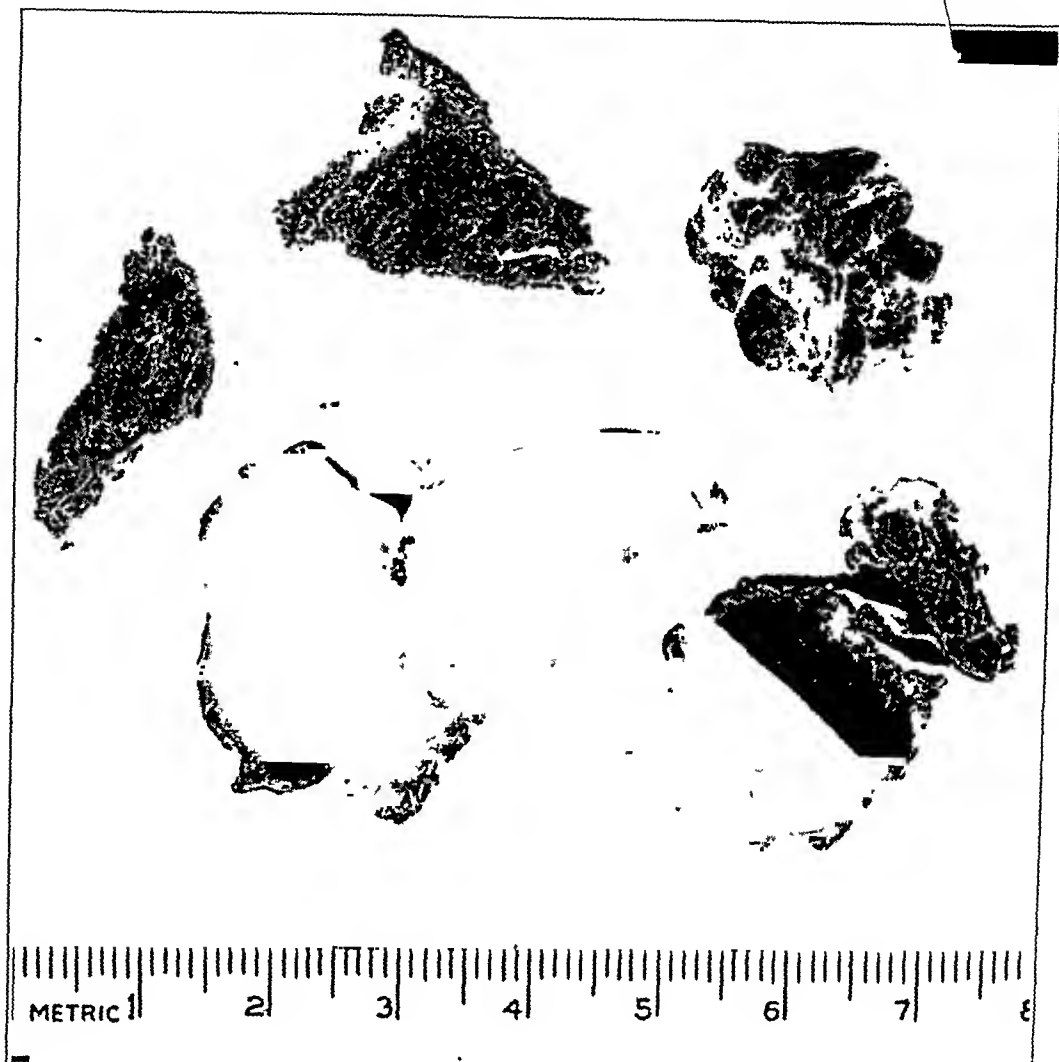


Fig. 2 (case 1).—Material removed from the inner compartment of the left knee joint. The upper three bodies are tags of hypertrophic synovial fringes. Of the lower three bodies, the middle one with the rounded edges was free within the joint; the other two, while loose, were still attached to the surface of the condyle, and formed the outer edges of the crater from which the free body was sequestered.

Second Attack—When next seen on October 4, the patient's left knee was again locked in flexion at 45 degrees. During the previous evening, "for no apparent reason," the knee joint locked. Marked tenderness and swelling were present over the internal anterolateral surface of the joint.

Operation was advised, and the patient was admitted to the hospital. He was operated on the following day.

Operation.—With the patient under nitrous oxide-oxygen anesthesia, a straight longitudinal incision was made to the inner side of the patella, and the inner compartment of the left knee joint was exposed. A large oval body with smooth rounded edges was found lying free within the joint. This body was removed, together with two irregularly shaped pieces of bone and cartilage which were partially separated from the inferior articular surface of the internal condyle. Several tabs of hypertrophied synovial villi were also removed. The wound was closed without drainage.

The patient was discharged on the fifteenth day after operation. He was free from pain and had a normal range of motion in the left knee joint. When last seen, three months after operation, there was no disability.

Gross Examination.—At the time of operation the conditions within the knee joint were carefully observed. There was a slight increase in the amount of synovial fluid. The internal semilunar cartilage was intact. No evidence of infection was noted.

The foreign body which was removed was ovoid and of the size shown in figure 2. It was glistening white, with smooth, rounded edges. The body consisted of a thick layer of articular cartilage and a thin, partially absorbed layer of subchondral bone.

The condition of the inferior surface of the internal femoral condyle was of interest. To the mesial side of the condyle and at a point near the attachment of the posterior crucial ligament was seen a large ovoid crater extending through the articular cartilage and into the bone of the condyle. This depression corresponded to the size and shape of the foreign body which was found free in the joint. The assumption is made that the foreign body was an extrusion of cartilage and bone from the site of the crater and that the crater was made by this extrusion. The margins of the crater were rounded; its walls were sheer; its depth was slightly greater than the thickness of the foreign body. The margins of the crater were loose on the anterior, internal-lateral and posterior sides. At operation, the already loosened cartilage about the crater with its attached bone was removed in two irregularly shaped pieces. The cartilage was friable and tore from its attachment to the remaining articular cartilage with ease, leaving a sloping, irregular and tufted edge. The defect which was produced by the removal of these two pieces of semidetached cartilage and bone, together with that of the crater, occupied practically the entire mesial half of the articular surface of the internal condyle.

Laboratory Examination.—Repeated blood counts, chemical determinations of the blood and urinalyses were consistently normal. The Wassermann reaction of the blood was negative. Bouillon and agar slant cultures of the fluid in the joint, a piece of hypertrophied synovial villi, and a portion of foreign body were free from bacterial growth after eight days' incubation.

Microscopic Examination.—The synovial villi (fig. 3) were large and their papillae broad. The surface lining consisted of a single layer of flattened cells; it was intact in some areas, but in others it was replaced by a thin, compact band of acid-staining fibrin. Immediately beneath the periphery were a large number of thin-walled blood vessels which were dilated and contained within their lumen an excessive number of polymorphonuclear leukocytes. The adjacent tissue was loose and edematous, and throughout it were scattered many plasmocytes and youthful connective tissue cells, together with an occasional polymorphonuclear

leukocyte. In the vicinity of the blood vessels were seen collections of lymphocytes. The deeper tissue had a normal fibro-areolar structure.

The diagnosis was: subsiding acute inflammatory changes in hypertrophied synovial villi.

The section of the foreign body consisted chiefly of cartilage to the under surface of which was adherent a small amount of bone. The cartilaginous surface of the section was smooth, and the nuclei of the cartilage cells in the first zone lay parallel to the marginal edge; in the second zone, the nuclei occupied an indefinite position, whereas in the deepest zone, they were arranged at right angles to the surface. The cartilage was viable and of normal composition.



Fig. 3 (case 1).—Photomicrograph of the hypertrophic synovial villi removed from the left knee joint. Hematoxylin eosin; $\times 61$.

The bone present in the free body was small in amount, and on section showed by its poor staining quality marked decalcification (fig. 4). No evidence of osteoblastic activity was found. The bone cells were few in number and necrotic. The margins of the trabeculae were irregular and fuzzy, while the presence of many marginal lacunae gave evidence of osteoclastic activity, although no osteoclasts were found.

The diagnosis was: necrotic subchondral bone undergoing decalcification and absorption.

In addition to the patient, two other male members of his family were said to have suffered from the same type of disability. These persons, the patient's father and paternal uncle, were examined. The records of their cases, which follow, verify and confirm the diagnosis of osteochondritis dissecans.

CASE 2.—H. E. H., a white man, aged 49, father of the patient, when 12 years of age first noted a slight, intermittent, dull pain in the joint of the left knee, accompanied by limitation of both flexion and extension. No history of preceding

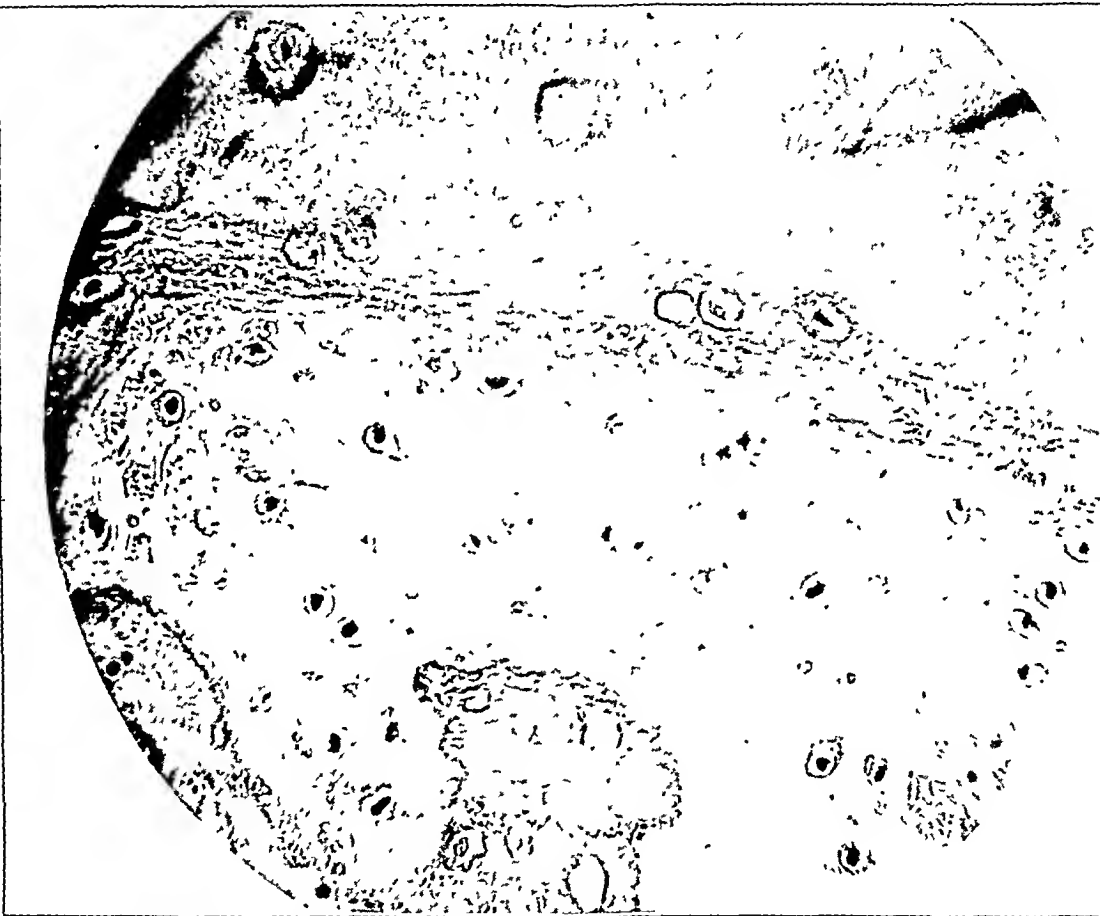


Fig. 4 (case 1).—Photomicrograph of the osteocartilaginous body removed from the left knee joint. Hematoxylin eosin; $\times 328$.

trauma could be obtained. Occasionally, following strenuous activity, the knee would swell and lock, but the patient was able to free the obstruction. Operation for the removal of a foreign body in the knee joint was recommended but refused. The condition persisted for twenty years. An apparent cure was effected by the spontaneous extrusion of the foreign body from the knee joint into the surrounding soft tissues.

At the present time, the patient is free from pain and disability. Examination revealed the presence of a hard mass beneath the outer edge of the quadriceps extensor femoris muscle just above the external condyle of the femur. A roentgenogram demonstrated this mass to be a piece of bone or cartilage, and in addition

showed that a smaller particle of bone or cartilage lay in the midanterior portion of the knee joint apparently attached to or embedded in the capsular ligament (fig. 5).

CASE 3.—G. W. H., a white man, aged 46, paternal uncle of the patient, when about 15 years of age noticed the development of "locking" of the joint of the right knee without a history of preceding trauma. The disability continued intermittently for thirteen years. The periods of limited function of the joint became more frequent and lasted longer as he grew older. Walking upstairs or climbing a hill predisposed to "locking" of the joint. Medical aid was sought, and operation was advised.



Fig. 5 (case 2).—Lateral view of the left knee joint. Two foreign bodies are seen; the upper lies beneath the lateral border of the quadriceps extensor; the lower lies in the midanterior portion of the joint.

On July 13, 1912, the patient was admitted to the Jefferson Hospital. An excerpt from the hospital records reads: "Diagnosis: floating body in the right knee joint. Physical examination negative, except the right knee which is slightly swollen at the inner aspect; the patella appears to float in fluid. The knee joint was opened by Doctor Despard under general anesthesia and a medium sized piece of bone removed. The patient was discharged in good condition on the sixteenth day after operation."

Since operation, the patient has been free from pain and disability. Roentgenographic examination of the right knee joint (Oct. 1, 1928) failed to show any abnormality of the bones or cartilage comprising the joint.

CASE 4.—*History*.—D. S. P.,² a white boy, aged 19, tall and well developed, was first seen on April 5, 1927. Three weeks previously, without assignable cause, the right knee became swollen. Any sudden twist caused pain in the region of the external lateral ligament, and several times a day the knee joint would "lock" and the patient could extend the leg only after manipulation. The discomfort increased in severity.



Fig. 6 (case 4).—Right knee joint; an osteocartilaginous body is loosened from the inferior surface of the internal femoral condyle.

Examination.—Motion at the knee was free; there was a slight amount of swelling present, and a point of tenderness over the attachment of the external lateral ligament was found.

A roentgenogram disclosed a large, partially detached sequestrum from the midarticular surface of the right internal femoral condyle (fig. 6).

Operation.—On April 20, with the patient under general anesthesia, the foreign body consisting of articular cartilage and subchondral bone was removed. The patient made an uneventful recovery.

2. Cases 4 and 5 concern private patients of Dr. DeForest P. Willard.

When examined in February, 1930, the patient complained of infrequent pain in the left knee. A roentgenogram revealed the presence of a solitary foreign body in the inner compartment of this knee.

CASE 5.—History.—W. P., Jr., a brother of D. S. P., white, aged 19, over 6 feet in height and weighing but 150 pounds (68 Kg.), was first seen on July 25, 1925. For several years he had complained of pain in both knees and in the dorsal and lumbar portions of the spine, following exercise.

Examination.—The left lower extremity was one-half inch (1.27 cm.) shorter than the right. A slight lumbar scoliosis to the left was present; both feet were pronated; posture was poor and the musculature weak.

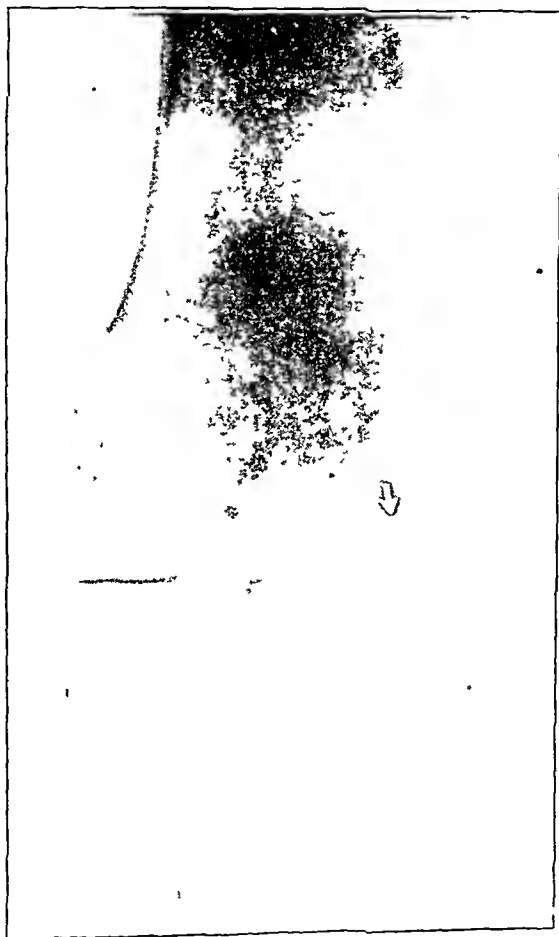


Fig. 7 (case 5).—Roentgenogram showing the presence of a loosened osteo-cartilaginous body from the inferior surface of the left internal femoral condyle.

When next seen, on Jan. 11, 1927, the patient complained of pain in both knees but more especially in the left, and frequent inability fully to extend the left leg. The joint of the left knee at times became swollen.

There was a slight grating but no swelling in the left knee joint. The ligaments were somewhat relaxed, and there was pain on pressure over the internal lateral ligament.

A small sequestrum from the middle portion of the articular surface of the internal femoral condyle was shown by roentgenogram to lie free in the joint of the left knee (fig. 7).

HEREDITY AS AN ETIOLOGIC FACTOR

The involvement by osteochondritis dissecans of more than one joint in the same person is uncommon. Bernstein, Blanco, Richards and Walter reported cases in which more than one joint in the same person was involved. When more than one joint is the site of osteochondritis dissecans, the involvement is frequently found to be bilateral.

Few references are made to heredity and familial or congenital factors as possibly being responsible for the development of this condition. Rieger spoke of "a predisposition." Kappis claimed that there may exist a congenital disturbance of the articular cartilage predisposing it to injury. Bernstein, in reporting the presence of osteochondritis dissecans of both knees of two sisters and a brother, stated that the disease is probably hereditary.

From a consideration of the cases here reported, it would seem that heredity should be considered as an etiologic factor in the occurrence of osteochondritis dissecans.

SUMMARY

1. The various theories of the etiology of osteochondritis dissecans found in the literature are abstracted.

2. Five case reports are given in which osteochondritis dissecans of the knee joint was found in various members of the same family, (*a*) in three men of one family; son, father and paternal uncle, and (*b*) in two brothers, in one of whom there was bilateral involvement.

CONCLUSION

Heredity operates as an etiologic factor in the occurrence of osteochondritis dissecans.³

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The bibliography here given was selected from 365 articles, and with the exception of 2 articles which were not available to us, we believe comprises the literature on the subject of osteochondritis dissecans. All the articles here listed have been abstracted.

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2008 Walnut Street.

THE CLOSED INTESTINAL LOOP

III. ASEPTIC END-TO-END INTESTINAL ANASTOMOSIS AND A METHOD FOR MAKING A CLOSED INTESTINAL LOOP SUITABLE FOR PHYSIOLOGIC STUDIES *

KARL H. MARTZLOFF, M.D.

AND

GEORGE E. BURGET, PH.D.

PORTLAND, ORE.

In order to carry on successfully a series of observations on hydrostatic pressure in closed intestinal loops¹ in dogs, as first demonstrated by Whipple and his associates,² it was necessary to develop some method whereby such loops could be made accessible while in an essentially normal environment. These loops have been so satisfactory for determinations other than hydrostatic pressure that we believe that the methods employed are worth reporting. We felt that any method devised should fulfil certain requirements. The loop should be wholly within the peritoneal cavity; its circulation should be normal which in turn would probably insure a normal mucosa over an indefinite period of time; its lumen should be accessible in unanesthetized animals for various types of observations; and the surgical technic necessary to accomplish this should be aseptic and within the ability of investigators accustomed to experiments on animals.

The technic devised is one that we now employ in the formation of a jejunal loop, and it differs only in minor detail for loops made at different levels of the small intestine. Dogs were used in all our work. Animals weighing over 15 Kg. are preferable in that they have small intestines of sufficiently large caliber to facilitate an end-to-end anastomosis. This, though not difficult, offers the only immediate technical difficulty which a little practice can readily overcome. Food was with-

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1. Burget, G. E.; Martzloff, K.; Suckow, G., and Thornton, R. C. B.: The Closed Intestinal Loop: I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal, *Arch. Surg.* **21**:829 (Nov.) 1930. II. Observations on Dogs with Jejunal and Ileal Loops with Blood Chemistry Findings, *Arch. Int. Med.* **47**:593 (April) 1931.

2. Stone, H. B.; Bernheim, B. M., and Whipple, G. H.: Intestinal Obstruction: A Study of the Toxic Factors, *Bull. Johns Hopkins Hosp.* **23**:159, 1912.

held from an animal for twenty-four hours before operation. One-half grain (32.4 mg.) of morphine sulphate and one one-hundredth grain (0.6 mg.) of atropine sulphate were given hypodermically one-half hour before ether narcosis was induced. The usual tincture of iodine preparation for the skin was employed.

OPERATIVE TECHNIC

An upper right rectus incision of suitable length (about 8 cm.) is made about 3.5 cm. from the midline. Treitz' ligament is identified and the jejunum traced

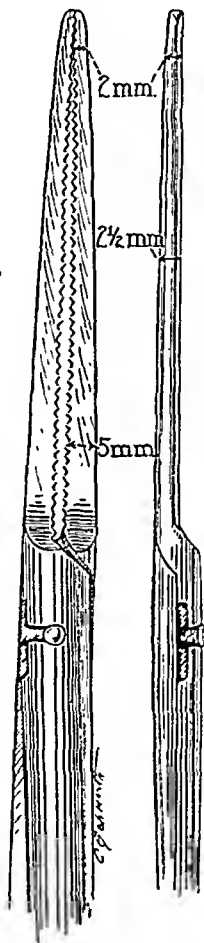


Fig. 1.—Drawing showing clamp with dimensions of the blades. The blades are 9 cm. in length. Note that the blades have some "spring" so that tips come together before the more proximal surfaces. This is done so that when the blades are entirely in contact there will be sufficient pressure at the tips, where the blades are weakest, to prevent the intestine from slipping. The longitudinal groove cannot be seen in this illustration. An ideally constructed clamp of this type should be tongued and grooved longitudinally and without the transverse serrations.

distally. The proximal point at which a jejunal loop can be made and survival anticipated is where the mesenteric veins from the contemplated intestinal segment enter the mesenteric root at right angles. This point varies in its distance from Treitz' ligament and can only be determined in a given animal by examining the

mesenteric root, putting the mesentery under tension and observing the color of the intestine. If one attempts to utilize a segment of jejunum the mesenteric veins of which tend to curve posteriorly as they enter the superior mesenteric vein, the possibility of some circulatory disturbance is considerably increased.

The length of the proposed jejunal loop is dependent on the amount of intestine supplied by a single primary mesenteric artery and vein. Our loops measured from 5 to 12 cm.; a length of 9 cm., however, was a general average. Four clamps are placed on the intestine at either end of the proposed loop. The clamps are applied in such order that the instruments (fig. 2, *C-1* and *C-2*) furthest removed from the end of the loop are placed first. The other clamps are then placed as shown in figure 2. The two most distal clamps are specially designed and will be described. It will be noted that they are placed to form an angle of about 75 degrees with the intestine to which they remain attached for the purpose of later establishing an anastomosis.

The special clamps are simple and inexpensive. It will be noted (fig. 1) that the bite of the clamp is from 2 to 2.5 mm. in width, so that a minimum of trauma-

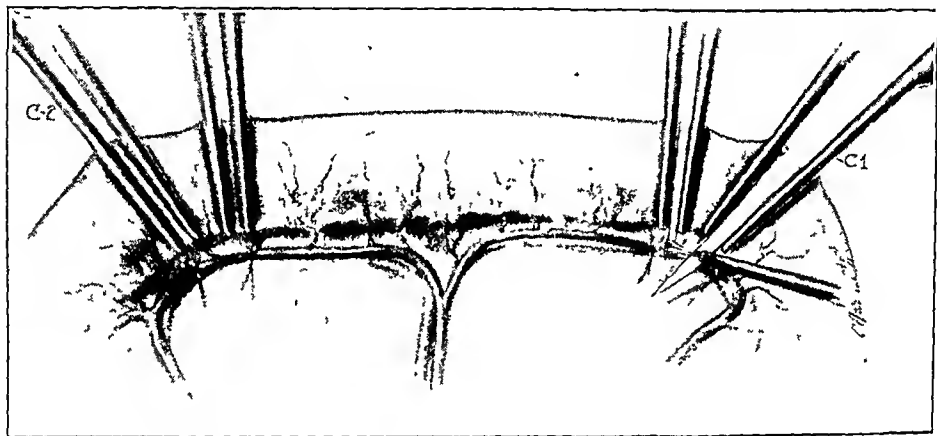


Fig. 2.—Clamps in place preparatory to section of the intestine. The two most distal clamps (*C-1* and *C-2*) are placed to form an angle of less than 90 degrees with the segment of intestine to which they remain attached.

tized tissue is involved in the intestinal anastomosis. One opposing surface is grooved longitudinally and the tips are smooth. More satisfactory, possibly, would be a clamp the opposing surfaces of which were tongued and grooved. For purposes of economy, we did not incur this additional expense. The lips are sufficiently long (9 cm.) to be used on intestine of any diameter and thick enough to insure uniform pressure from tip to base. In our earlier experiments Kocher clamps were used throughout. At times we found them a little short for intestines of larger caliber. The handles were short, so that the assistant's hands were in the way, and the teeth at the tips of the lips were inconvenient when the clamps were removed from the ends of the sutured intestine. The instrument described has overcome these objections.

When the instruments are placed, as shown in figure 2, the vascular arches are ligated and the intestine and mesentery are sectioned with an electrocautery. The ends of the loop are then closed in two tiers with a Parker-Kerr suture of number 00 plain catgut. This suture technic is adequate to withstand a hydrostatic pressure sufficient to rupture the loop at any time after operation. The

loop is then temporarily placed in the peritoneal cavity and the end-to-end anastomosis performed by an aseptic technic.

ASEPTIC TECHNIC FOR END-TO-END INTESTINAL ANASTOMOSIS

To one familiar with the various methods of aseptic end-to-end intestinal anastomosis, it will be apparent at once that no real originality enters into our method. It is merely a modification of methods previously described.

Without trying to enumerate the various writers who have contributed to the clamp technic of aseptic end-to-end intestinal anastomosis, in contradistinction to the bulkhead method or methods employing special mechanical contrivances such as rubber balloons, rings, cones, etc., we believe that two require special mention. Rostowzew³ described a technic requiring special and cumbersome clamps which were left on the ends of the divided intestine until the necessary Lembert sutures were in place, when the clamps were removed. The cauterized ends of the intestine remained closed while the previously placed sutures were tied. It should be noted that in Rostowzew's method the ends of the intestine to be united were held not directly end-to-end, but at right angles to the longitudinal axis of the intestine, producing a greater inturning on one side than on the other.

Moszkowicz⁴ employed the same technic, with slight mechanical changes, and finally devised a three bladed clamp which, in a far simpler manner, performed the function of the cumbersome instrument first employed by Rostowzew and himself. The technic and instrument described by Rankin⁵ nearly twenty years later is in all essential respects the method of Moszkowicz, who was not mentioned by Rankin.

Parker and Kerr⁶ described their method of closing both ends of the sectioned intestine by placing "basting stitches" over each of the occluding clamps. These sutures are pulled taut after the clamps are removed and invert the crushed ends of the intestine. The sutures designed to anastomose the two occluded ends of the intestine are then placed and tied, and finally the lumen is reestablished by withdrawal of the previously placed "basting stitches."

All of the clamp methods of aseptic end-to-end anastomosis since described have utilized the features of Rostowzew's operation, as modi-

3. Rostowzew, M. I.: Aseptische Darmnaht, Arch. f. Chir. **82**:462, 1907.

4. Moszkowicz, L.: Ueber aseptische Darmoperationen, Wien. klin. Wchnschr. **21**:1593, 1908; Ueber aseptische Darmanastomosen, ibid. **22**:848, 1909.

5. Rostowzew, M. I.: Aseptische Darmnaht, Arch. f. klin. Chir. **82**:462, 1907. Gynec. Obst. **47**:78, 1928.

6. Parker, E. M., and Kerr, H. H.: Intestinal Anastomosis Without Open Incisions by Means of Basting Stitches, Bull. Johns Hopkins Hosp. **19**:132, 1908.

fied by Mosckowicz, while some have utilized the principles of the Parker-Kerr method.

Pringle⁷ and Scarff⁸ eliminated in their methods the angulation of the ends of the intestine, which is the basic objection to the Rostowzew-Moskowicz operation, by bringing them into direct apposition. This eliminates the turning in of intestinal spurs of unequal length and also the carrying of sutures across the end of cauterized intestine. However, in both technics mattress sutures are inserted while the clamps are still in place. In our experience, this procedure makes it difficult to place the mattress sutures accurately; occasionally opposite walls of the intestine are sutured together. In order, then, to reestablish the intestinal lumen at the line of anastomosis, the occluding suture must be removed with a resultant break in asepsis.

The advantages that we have experienced in our modified technic as compared with the others that we have used are: 1. A minimal amount of tissue (from 2 to 2.5 mm.) is devitalized with the instrument described. 2. The first row of Parker-Kerr sutures does not cross the end of cauterized intestine and is placed so close to the clamps that it adds about an additional millimeter to the inturned flange. 3. The ends of the Parker-Kerr sutures, when tied, allow ready manipulation of the intestine with minimal trauma and the accurate placing of mattress sutures. In the forty-one dogs and two patients on whom this identical technic was used, the intestine was not transfixed, healing was uneventful, except as noted, and obstruction at the site of anastomosis occurred in one dog.

Leakage at or near the site of anastomosis occurred in three animals: (1) in a duodenal anastomosis in which the ends of intestine were brought together under tension and a round worm was burrowing through at the suture line; (2) in an anastomosis in which the intestine distal to the line of suture was plugged with worms and a worm was coming through the line of anastomosis, and (3) about 1 cm. proximal to the line of suture in a dog that died, as did the other two, of a peritonitis secondary to the rupture of the intestinal loop.

In eight other dogs not included in the previously noted forty-one, we used number 0 catgut for our Parker-Kerr basting stitches and found leakage in two, so the use of catgut was abandoned.

Obstruction at the site of anastomosis occurred in one animal (no. 91) which lived for six weeks. This was due to a thick adhesion on one side of the anastomosis which prevented the inturned flange from unfolding as it had on the opposite side. It should be remembered that in

7. Pringle, S.: Aseptic Resection of the Intestine, *Brit. J. Surg.* **12**:238, 1924.

8. Scarff, J. E.: Aseptic End-to-End Suture of the Intestine, *Ann. Surg.* **83**:490, 1926.

many of our animals a peritonitis of varying duration occurred, owing to damage to the closed intestinal loops, so that the intestinal anastomoses were often exposed to surroundings that favored infection, inflammation and adhesions.

We used the technic described by Scarff in forty-seven dogs. A leak, not caused by worms, developed at the site of suture in eight, so we adopted the method described here.

The anatomic details of our operative results will be given in another paper. The technic employed by us is as follows:

Technic.—The two special clamps are brought together and rotated in their longitudinal axes so that their uneven surfaces are face to face. A continuous

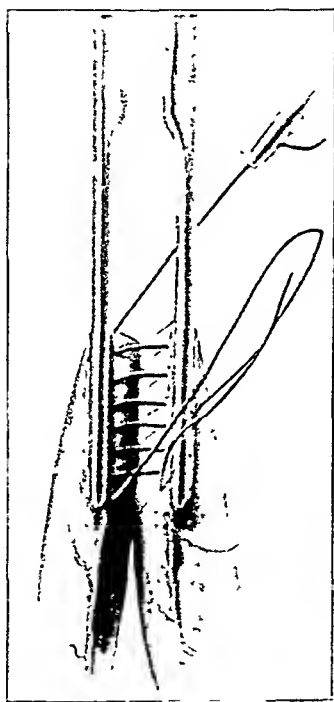


Fig. 3.—Specially designed clamps rotated in their longitudinal axes so that the first Parker-Kerr suture can be placed.

right-angled serosubmucosal suture of number 0 black silk on a curved intestinal needle is placed in the two opposing intestinal walls as close to the clamps as possible (fig. 3). The sutures should begin on the antimesenteric margin of one intestinal segment and terminate on the mesenteric border. The free ends are secured, the clamps are rolled so that their even surfaces are opposed and a similar suture is placed so that it begins and terminates on sides of the clamps opposite to its counterpart, as shown in figure 4.

The anastomosis clamps are now removed, one at a time, while both ends of the sutures are held slightly taut (fig. 5). When the last clamp is off, the sutures are pulled tightly and tied snugly enough to narrow the diameter of the anastomosis by 1 or 2 mm. (fig. 6) in order to invert the crushed intestine at both the mesenteric and the antimesenteric margins. During this manipulation the cauter-

ized end of the gut does not open when the clamp described is used, and no difficulty is experienced with the mesenteric aspect of the intestine.

The ends of the previously placed sutures now serve as stay sutures with which the intestine can be rotated in its longitudinal axis. The first line of sutures is now reenforced by a second row of closely placed Halsted mattress stitches of 0 black silk on milliner's needles (fig. 7). At first we left one long suture on opposite sides of the anastomosis in order to apply traction and thereby assure the patency of the lumen. This was done because with Scarff's technic it occasionally happened that one or two sutures penetrated to the opposite intestinal wall, thereby closing the lumen. This necessitated the removal of the faulty stitches with consequent breach of asepsis. With the present method the foregoing has never occurred. We have abandoned the use of these accessory traction

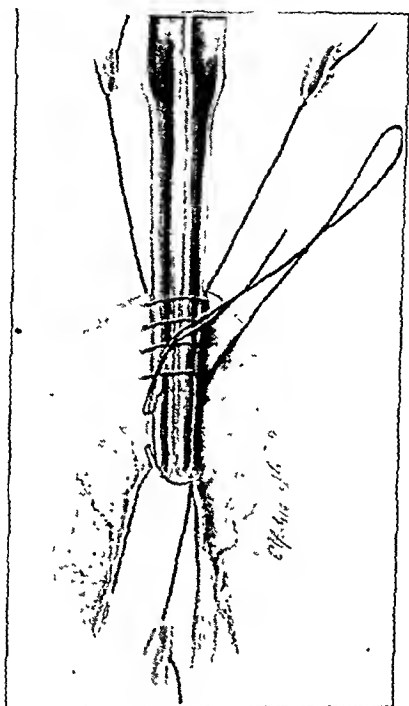


Fig. 4.—The clamps have been rotated so that their flat surfaces are in apposition and the second Parker-Kerr suture is being placed.

sutures and never invert the intestine through the anastomatic lumen to insure its patency. The mesenteric defect is closed with interrupted fine black silk sutures.

Method of Fixing the Loop.—The loop is again brought out of the peritoneal cavity and laid over the lateral margin of the incision. Allis clamps are placed on the peritoneum of the medial aspect of the incision, traction is exerted and the midline fatty appendage is dissected medially to the linea alba the length of the incision. This denuded area is further traumatized by rubbing it with dry gauze.

The middle two thirds to three fourths of the loop is sutured (figs. 8 and 9) as closely as possible to the right of the linea alba with number 0 interrupted black silk on curved intestinal needles, care being taken not to penetrate the submucosa too deeply, to prevent subsequent rupture of the loop at the point of suture. It is preferable to err on the side of safety and suture only the intestinal muscularis. In our experience, all loops so attached have adhered to the anterior abdominal wall.

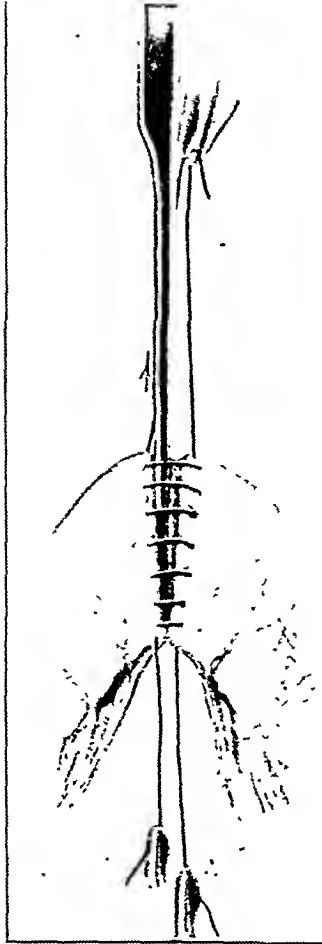


Fig. 5.—The last clamp is being withdrawn leaving two narrow segments of crushed intestine in direct apposition. The sutures are placed closer to the crushed end of the intestine than the illustration shows.

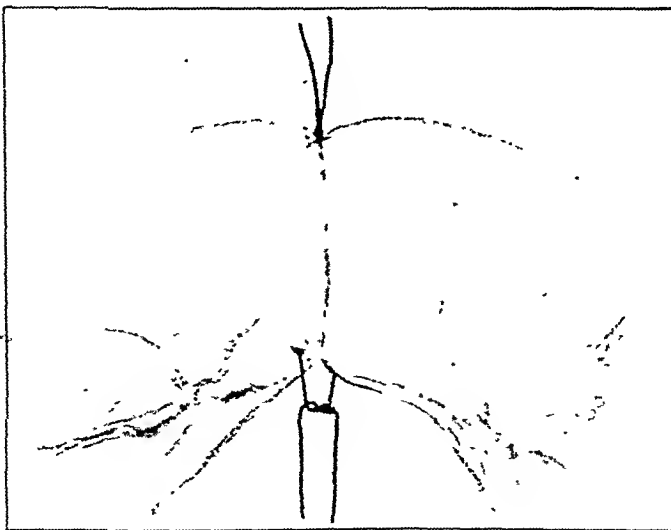


Fig. 6.—The two Parker-Kerr₂ sutures have been drawn taut and tied. The cauterized ends of the intestine remain closed during the entire procedure.

A guide of linen is next placed in the skin of the anterior abdominal wall to the left of the midline at a level where the loop can be reached by a hollow needle passed through the abdominal wall just to the right of the linea alba.

The wound is closed with catgut and heavy linen and no dressing is applied. The dog is given water after the third day and milk and hamburger steak on the fifth day. Skin sutures are removed on the fifth day.

CARE OF ANIMAL AFTER OPERATION

As essential to the survival of the animal as the proper operative technic is the postoperative care of the closed loop. It should be tapped just to the right of the midline at a point opposite the linen guide suture under aseptic precaution with a number 19 needle on a syringe, from eighteen to twenty-four hours after operation and every twenty-four hours thereafter until no further secretion is obtained. Aspiration is facilitated by the postoperative anesthesia of the abdominal wall between

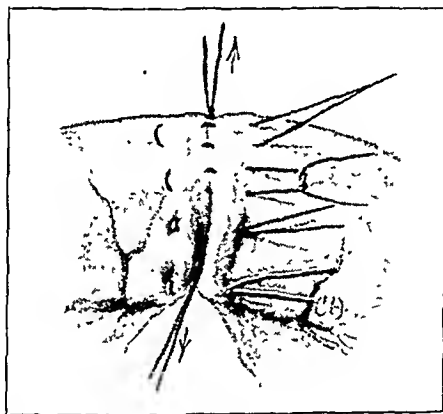


Fig. 7.—Halsted mattress sutures of fine black silk on milliner's needles are used to complete the anastomosis. The sutures are placed somewhat more closely than is depicted in the illustration and need not be "reenforced," for this suture line is adequate when properly placed.

the incision and the linea alba. This lasts for months and the animals are entirely docile while being manipulated. It is advantageous after aspiration of the contents of the loop to wash the loop with physiologic solution of sodium chloride. We believe that this hastens restoration of the loop to normal by removing the inflammatory products incident to the operative trauma.

There is considerable variation in the behavior of the loops. After three or four aspirations and washings some may go for varying periods before this again becomes necessary.

When loops are made lower in the small intestine, aspiration need not be instituted so soon after operation. Provided the loop is one that survives and will be suitable for various types of observation, this may be commenced when the sutured ends have sloughed and healed over,

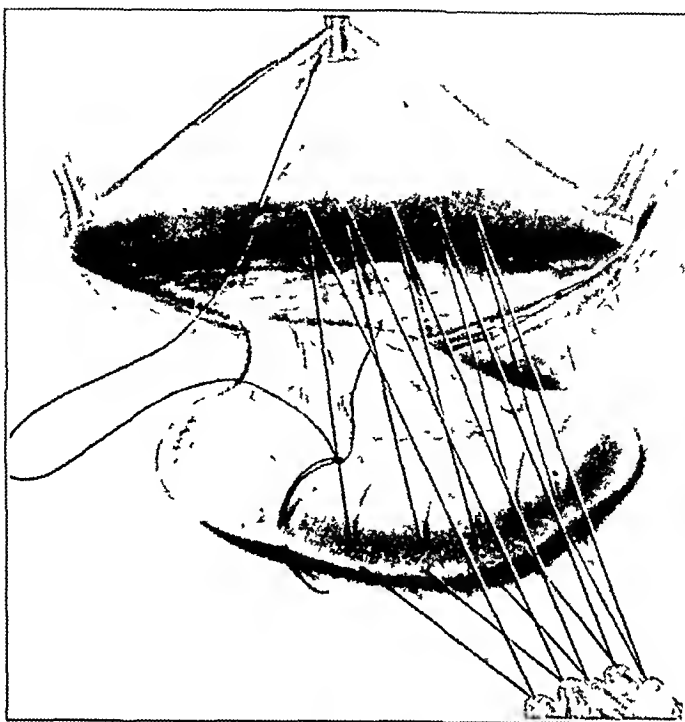


Fig. 8—Sutures are placed but not tied.

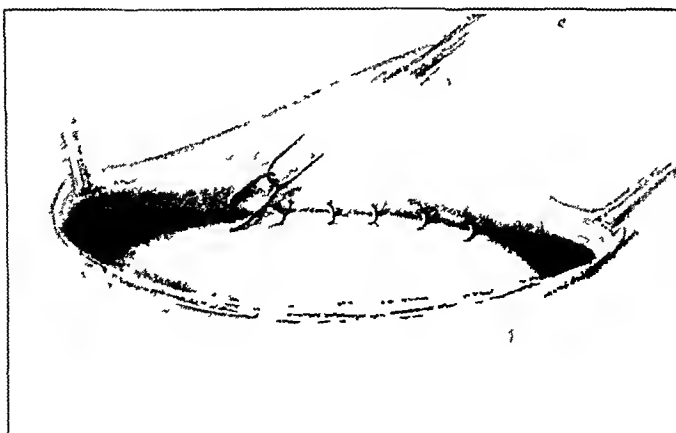


Fig. 9—Loop sutured in place. Sutures are carried sufficiently near to the ends to prevent bagging when the loop is being aspirated.

which requires a period of from ten to fourteen days. As previously noted, various loops, even though destined to survive, require aspiration at various intervals. In the case of loops that have not become distended for some time, our first clue that the animal has a distended loop is its loss of appetite, lack of animation and increase in temperature. Almost immediately after the intraloop pressure is relieved, the animal is spirited and will take food.

When one desires to use a loop that has not been aspirated for some time for studies of digestion or absorption, it is necessary to aspirate and wash the loop a day or two previously in order to free it from the epithelial and bacterial residue. In old loops that have not been disturbed for several weeks there is a gradual accumulation of a grayish, putty-like material which, after several months, will entirely fill the loop.

This procedure was carried out on ninety-two dogs. Some of the animals lived for months, in one instance for over one year, without aspiration of the loop except for a few days after operation; others, again, had to be aspirated at intervals varying from days or weeks, to months, and some of these have been living for a year or more.

We found that solutions injected into these closed loops can be aspirated so successfully that all but 1 cc. or a fraction thereof can be recovered.

Over a period of about a year animals with closed intestinal loops were subjected to various determinations of blood chemistry, the loop contents were studied bacteriologically, and observations on digestion and absorption were made with cane sugar, levulose, fats and peptones.

VALUE FOR PHYSIOLOGIC INVESTIGATION

It is evident, we believe, that this type of loop presents unusual possibilities for various types of observations, in that it overcomes some of the shortcomings present in the other experimental methods. As compared with the intestinal loop lying in the peritoneal cavity of anesthetized and decerebrate animals, our method has the advantage of not being an acute experiment under anesthesia while our determinations are not made on recently traumatized intestine. This method also overcomes the objection inherent in the use of closed surviving intestinal segments suspended in Tyrode's or Locke's solution in that our loops are viable, in a normal environment, and can be used repeatedly.

The Thiry-Vella fistula technic and the polyfistula method of London⁹ have definite shortcomings in that they produce fistulas, subject to secondary infection and abnormal exposure to atmospheric pressure.

9. London, E. S., in Abderhalden: *Handbuch der biologischen Arbeitsmethoden*, Vienna, Urban & Schwarzenberg, 1926, vol. 6, pp. 491 and 544.

They also present the factor of error due to difficulty in recovering *in toto* the remains of injected solutions; the polyfistula method brings in an additional phenomenon of motor function, which is undesirable for some determinations. The method devised obviates, either altogether or in a large measure, the foregoing experimental difficulties in that it provides a fixed and accessible closed loop in a normal environment which affords a histologically normal mucosa in a fairly large percentage of animals. Finally the unabsorbed residue of solution injected into such a loop is recoverable to within approximately 1 cc. of its total volume. During experiments on the digestion of levulose we have also performed laparotomy and aspirated blood from the mesenteric vein of the loop for simultaneous comparison with the heart's blood. These and other observations are being prepared for publication.

SCALENIOTOMY IN THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS *

JOSEPH W. GALE, M.D.

AND

WILLIAM S. MIDDLETON, M.D.

MADISON, WIS.

In 1822 Carson¹ sounded the keynote to the surgical treatment of pulmonary tuberculosis when he said, "It has long been my opinion that if ever this disease is to be cured, and it is an event of which I am by no means disposed to despair, it must be accomplished by mechanical means, or in other words by a surgical operation." There have since been evolved, roughly speaking, two types of operative procedure in these cases. The first type includes extrapleural paravertebral thoracoplasty suggested by Brauer² and performed by Friedrich in 1907, in which they advocated an extremely radical operation which carried with it a high mortality. However, the technic was soon modified by Wilms³ and Sauerbruch,⁴ but even to the present time it continues to carry many disappointing results, both in the immediate effects and later in the resultant spread of the disease in the contralateral lung.

In the second type are classed several conservative procedures, including artificial pneumothorax, first instituted by Potain⁵ in 1880. Artificial pneumothorax will not be considered in this report. Extrapleural pneumolysis was performed by Tuffier⁶ in 1883, phrenicotomy

* Submitted for publication, Sept. 25, 1930.

* From the Departments of Surgery and Medicine, University of Wisconsin Medical School.

1. Carson, J., cited by Riviere in *Essays Physiological and Practical*, Liverpool, F. B. Wright, 1822.

2. Brauer, L.: *Erfahrungen und Ueberlegungen zur Lungenkollapstherapie*. Die ausgedehnte extrapleurale Thorakoplastik, *Beitr. z. Klin. d. Tuberk.* **12**:49, 1909.

3. Wilms, M.: Die Pfeilerresektion der Rippen zur Verengerung des Thorax bei Lungentuberkulose, *Therap. d. Gegenw.* **54**:17, 1913.

4. Sauerbruch, F., and Ehring, H.: Die extrapleurale Thorakoplastik, *Ergebn. d. inn. Med. u. Kinderh.* **10**:869, 1913.

5. Potain: Des injections intrapleurales de l'air stérilisé dans le traitement des épanchements pleuraux consécutifs au pneumothorax, *Bull. Acad. de méd.* **19**:537, 1888.

6. Tuffier, T., cited by Alexander in *L'Etat actuel de la chirurgie intrathoracique*, Paris, Masson et Cie, 1914, pp. 90-105; 163-172.

by Stuert⁷ in 1911 and by Felix⁸ in 1922, intrapleural pneumolysis by Jacobaeus⁹ in 1913, and multiple intercostal neurectomy was introduced by Alexander¹⁰ in 1929. Of these, phrenicotomy is the most frequently used, and it is the simplest of the operative procedures. It is attended by a low rate of mortality, and until recently has been used merely as an adjunct to paravertebral thoracoplasty. Of late, however, this procedure has been proved by Matson¹¹ to have a marked therapeutic value of its own in the arrest of pulmonary tuberculosis, in addition to its adjunctive or test value. Up to the present when phrenicotomy as an independent procedure has been considered inadequate no recourse has been available other than the most radical type of operation, namely, paravertebral thoracoplasty. Therefore it seemed logical to seek some means of enhancing the value of phrenicotomy in order to produce the arrest of the disease without relinquishing the more conservative procedures.

Intercostal neurectomy and phrenic block are operative through the interruption of the motor nerves to important muscles of respiration. For an understanding of the rationale of such procedures, it is necessary to comprehend the contribution of these muscles to the mechanics of respiration. In his convincing clinical and experimental studies, Hoover¹² assigned certain definite values to the scaleni, the intercostal muscles and the diaphragm in respiration. Briefly stated, this observer concluded that the scaleni anchor the first ribs for the action of the upper three intercostal groups. Through their influence the intercostal muscles tend to bring about a bucket-handle movement of these ribs. The net result of this action is to induce an increase in the lateral and the anteroposterior dimensions of the thorax; but, if unopposed, such

7. Stuert: Künstliche Zwerchfellähmung bei schweren chronischen einseitigen Lungenerkrankungen, *Deutsche med. Wchnschr.* **37**:2224, 1911.

8. Felix, W.: Anatomische, experimentelle und klinische Untersuchungen über den Phrenikus und über die Zwerchfellinnervation, *Deutsche Ztschr. f. Chir.* **171**:283, 1922.

9. Jacobaeus, H.: Endopleurale Operationen unter der Leitung des Torakoskops, *Beitr. z. Klin. d. Tuberk.* **35**:1, 1916.

10. Alexander, J.: Multiple Intercostal Neurectomy for Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **20**:637, 1929.

11. Matson, R. W.: Exaeresis of the Phrenic Nerve in the Treatment of Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **22**:1, 1930.

12. Hoover, C. F.: The Functions of the Diaphragm and Their Diagnostic Significance, *Arch. Int. Med.* **12**:214 (July) 1913; Diagnostic Signs from the Scaleni, Intercostal Muscles and the Diaphragm in Lung Ventilation, *Arch. Int. Med.* **20**:701 (Nov.) 1917; The Functions and Integration of the Intercostal Muscles, *Arch. Int. Med.* **30**:1 (July) 1922; Respiratory Excursion of the Thorax, *Oxford Medicine*, New York, Oxford University Press, 1918, vol. 2, p. 29.

a function would result in the shortening of the longitudinal axis of the thorax. Accordingly, the pistonlike descent of the diaphragm on inspiration preserves this longitudinal dimension. Further important clinical observations were made by Hoover on the movements of the costal margin, normally and under pathologic conditions. For the present purposes these may be summarized briefly in the statement that normally the movement of the costal borders on inspiration is slightly outward. The diaphragm tends to pull the costal margins inward, and the antagonism of the scaleni and the intercostal muscles is expressed in their outward, upward pull. The scalene-intercostal group of muscles is more advantageously placed from a mechanical standpoint, and the resultant force represents the algebraic sum of the two in a slight outward movement of the costal margins on normal inspiration. As Hoover emphasized, variations in the undulatory movements of the upper ribs and in the excursions of the costal margins afford valuable diagnostic information as to underlying pathologic conditions.

Abundant evidence has accumulated to render judgment in the case of phrenic block, temporary or permanent. The logic of intercostal neurectomy would seem well grounded. From an anatomicophysiologic standpoint, it has seemed remarkable that the important scalene group should have escaped surgical attention.¹³ Certainly Hoover¹⁴ gave ample evidence of their mechanical importance. By clinical cases and experimental division of the scaleni, he was able to demonstrate a caudad movement of the unsupported first rib on inspiration, together with the manubrium, the second and the third ribs. Under such conditions, the fourth rib remained stationary, and not until the fifth rib was reached did the customary undulatory movement appear. From this level downward, the normal bucket-handle movement was exaggerated. Two children with cervical Potts' disease leading to paralysis of the scaleni have been studied in the Wisconsin General Hospital. In both of the patients the classic picture afforded by Hoover was confirmed. The most striking features were the caudad movement of the upper three ribs and the exaggerated outward movement of the costal margins on inspiration. Fluoroscopic examination established the motility of the

13. In qualification of this statement, attention is directed to the suggestion of Coffey (Northwest Med. 28:108 [March] 1929) that division of the scalenus anticus and medius affords a most advantageous approach for resection of the anterior arc of the first rib, and to that of Grégoire (Paris méd. 1:265, 1930) which utilizes scalene section as an adjunct to apical extrapleural pneumolysis. Neither of these observers has been interested in the essential motor phenomena of scalene activation.

14. Hoover (footnote 12, second, third and fourth references).

diaphragm in both of these subjects, although the sharp outward movement of the costal margins had led to a suspicion of an associated phrenic paralysis. Hoover further observed that in quiet inspiration the scaleni do not elevate the first ribs, but by their tone they neutralize the caudad tendency of intercostal contraction in this location. In one of his clinical patients¹⁵ in whom intercostal paralysis had occurred, the scaleni were capable of inducing a cephalad movement of the sternum and first upper pair of ribs on quiet as well as deep inspiration. On forced inspiration this subject could increase the circumference of the thorax $\frac{3}{4}$ inch (19.05 mm.) at the third and at the sixth interspaces through scalene action. From these observations, the scaleni would seem to afford an unusually advantageous point of attack for immobilization of the pulmonary apices.

The scaleni are three (rarely four) muscles of the deep cervical group. They arise from portions of the transverse processes of the third, fourth, fifth, sixth and seventh cervical vertebrae and insert by tendinous bands into the first and second ribs. Their origins are concealed by the sternocleidomastoid muscle, but their insertions are more widely separated. The largest and longest of these muscles is the scalenus medius, followed in order by the anticus and posticus. The scalenus anticus inserts into the scalene tubercle on the upper surface of the first rib. Rarely, this insertion is split by the subclavian artery, and two distinct muscles are formed. The lateral muscle is then known as the minimus. The scalenus medius inserts into the upper surface of the first rib at about a centimeter posterior to the insertion of the anticus. Some fibers may extend forward and insert into the upper edge of the second rib. The scalenus posticus inserts into the outer surface of the second rib. The nerve supply to these muscles is derived from the cervical plexus, and the posticus may receive branches from the brachial plexus.

The surgical approach used for the division of these muscles is somewhat similar to the one employed in the approach through the subclavian triangle of the neck for exposure of the phrenic nerve. Owing to the origin of these muscles through numerous tendinous slips from the transverse processes of the lower cervical vertebrae, approach at this point is necessarily rendered difficult and inadvisable. The points of insertion into the first and second ribs, however, are through tendons that are easily identified when the other structures are carefully retracted. It is because of their accessibility at this point that the section of each muscle is made near its insertion.

15. Hoover (footnote 12, fourth reference).

TECHNIC

- The patient is given a preliminary dose of $\frac{1}{6}$ grain (0.01 Gm.) of morphine sulphate and $\frac{1}{150}$ grain (0.0004 Gm.) of scopolamine two hours before operation. The same dosage is repeated one hour later or one hour before operation. The position on the operating table is important to effect the best exposure. The patient is placed in the supine position, with his head turned as far as possible to the side opposite to the operative field. Sand bags or other measures to elevate

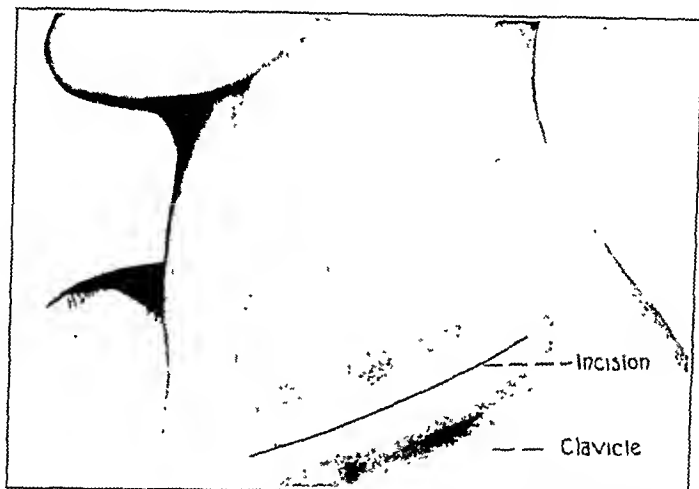


Fig. 1.—The illustration shows line of incision infiltrated with procaine hydrochloride anesthesia. Note the line of the incision about 1.5 cm. above the clavicle.

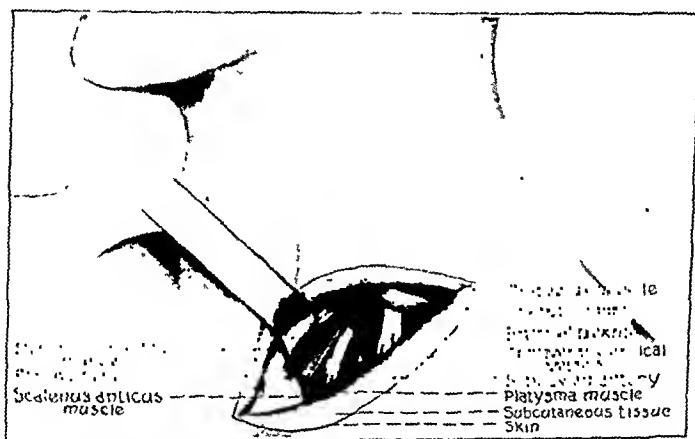


Fig. 2.—The illustration shows the scalenus anticus muscle with the overlying phrenic nerve exposed by retraction forward of the posterior belly of the sternocleidomastoid muscle.

the head or shoulder are inadvisable, since such manipulations tend to relax the scaleni. Rotation of the head to the opposite side, however, has two distinct advantages in that the sternocleidomastoid muscle is thrown forward, and the scaleni are placed under tension. The operative field is thoroughly prepared and draped. A 0.5 per cent solution of procaine hydrochloride is used. A wheal, extending from the posterior edge of the sternocleidomastoid muscle about 1.5 cm. above the clavicle backward to the anterior edge of the trapezius muscle, is

raised in the skin. The subcutaneous tissue and platysma muscle are thoroughly infiltrated, care being taken not to inject any of the solution into the external jugular vein that crosses the line of incision. This procedure requires from about 15 to 20 cc. of the solution. After five minutes the incision in the skin is made along the line of infiltration, following one of the skin folds. Little bleeding occurs on incision of the skin and superficial layers. The deep cervical fascia is then carefully divided, exposing the fatty tissue which is rich in blood supply. By careful blunt dissection the inferior belly of the omohyoid muscle is brought

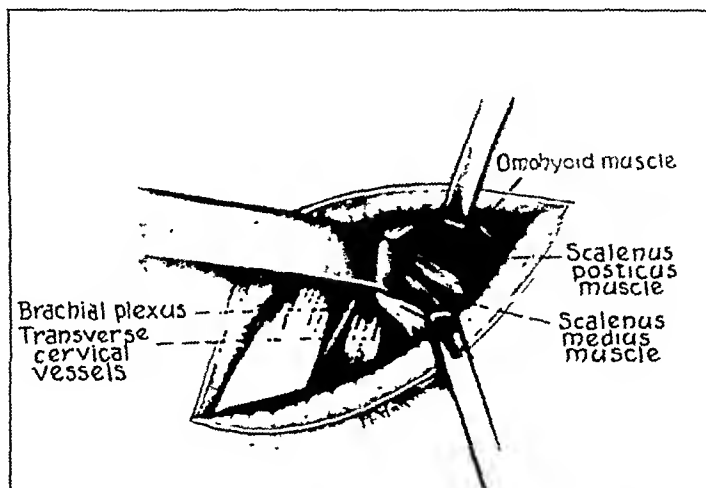


Fig. 3.—The brachial plexus retracted forward, the omohyoid muscle upward and the transverse cervical vessels downward, exposing the scalenus medius and the scalenus posticus muscles.

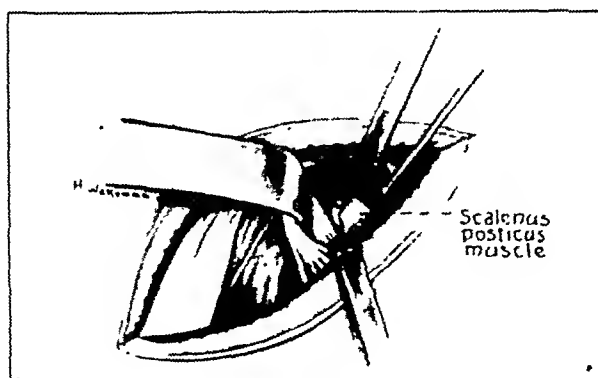


Fig. 4.—Same exposure as figure 3, showing the scalenus posticus muscle ready for division.

into view. This muscle serves as a useful landmark; the anterior portion, as it passes beneath the sternocleidomastoid muscle, overlies the scalenus anticus, which can be well demonstrated at this point by having the patient attempt to lift his head from the pillow. This movement brings all of the scaleni into relief by increasing their tension. Just above the point of crossing the sternocleidomastoid and the omohyoid muscles, the phrenic nerve will be seen on the anterior surface of the scalenus anticus directly beneath the muscle sheath. This also serves as a further useful landmark. About 1 cm. posterior to the insertion of the scalenus

anticus will be found the insertion of the larger scalenus medius. Lying between these muscles close to the first rib is the subclavian artery. The scalenus posticus is in close apposition to the medius, and it is not always possible to identify positively each as a separate muscle.

In exposing these muscles, care must be taken not to injure the brachial plexus or the transverse cervical vessels. By careful retraction this can be done without pain to the patient. When all the insertions are located, each muscle is infiltrated with a small amount of the procaine hydrochloride solution. They are then gradually separated from the surrounding structures until a straight aneurysm needle can be hooked beneath them. For dividing the muscles, the cautery knife is superior to the scalpel. Because of the coagulating effect of the former, there is little or no bleeding. During the division of the several scaleni, all important adjacent structures must be protected. Following their division, the field is carefully inspected for hemostasis, and the deeper layers are then closed by interrupted sutures of 0 plain catgut in the platysma muscle. The skin is sutured with a running subcuticular stitch, which is removed on the fifth day leaving an inconspicuous hair line scar. If the field is not entirely dry, a small rubber drain may be inserted, so that the excessive oozing of serum and blood will not collect beneath the skin. This drain should be removed after the first twenty-four hours.

INDICATIONS FOR OPERATION

The indications heretofore given for phrenic block have been numerous and diversified, but the results obtained depend on certain anatomico-physiologic alterations occurring within the thorax. At first it was thought that paralysis with subsequent rise of the diaphragm would benefit only basal lesions through compression. Time has proved this idea fallacious, because far removed lesions throughout the lung are benefited. This would not be true if the paralysis and the rise of the diaphragm induced merely compression phenomena. There is also a relaxation of the lung with a resultant contraction. The vital capacity is temporarily lowered, but this is soon compensated largely by the opposite lung. The other important muscles of respiration continue to function, and in these persons there is increased intercostal and scalene activity. The chief therapeutic effect is realized through the diminution in the size of the thorax in the longitudinal axis and in the relaxation of the affected lung. Further evidence of these circumstances is manifest by results which show that the degree of improvement is in direct proportion to the extent of rise of the paralyzed diaphragm. In the cases in which this rise is limited by complicating costophrenic adhesions, the results have been disappointing in the main. Rest is an enemy of tuberculosis, and when beneficial results have been produced by therapeutic measures where this is not the chief factor, its addition should enhance their value. It seems especially important that the remote apical lesions due to previously mentioned respiratory phenomena should be benefited by this adjunct. The performance of simultaneous scaleniotomy and phrenic block seems from anatomico-

physiologic considerations to be a logical procedure which does not depart in principle from the more conservative operations, namely, phrenic block and intercostal neurectomy. If phrenic block is carried out simultaneously with scaleniotomy, it is better to delay the former to the end of the combined operation to avoid the pain resultant from the evulsion of the nerve.

Up to date, in seven cases, patients have been subjected to scaleniotomy. In the first two cases, phrenic block was followed by scaleniotomy one week later. In the remaining five cases a combined operation was done. In every case there was a marked reduction in the respiratory excursion of the upper portion of the thorax. The caudad movement of the upper three ribs, which was recorded by Hoover on scalene paralysis or experimental section, has not been seen in any of these seven patients. An important observation in the five instances of combined scaleniotomy and phrenic exeresis was the constant absence of the increased upper intercostal movement, so commonly seen when the phrenic nerve alone is blocked or evulsed.

These patients showed very little reaction following operation, and suffered little or no discomfort, except for a slight temporary stiffness of the neck with some limitation of motion owing to pain during the first twenty-four hours. This was not severe enough to necessitate a sedative. In one case a hematoma developed forty-eight hours after operation. This complication has not occurred since the cautery has been used for division of the muscles. There has been no resultant sign of deformity or permanent restriction of motion of the head and neck. In the cases in which the operation was done in two stages, scaleniotomy following phrenic block, the vital capacity showed a decrease of from 8 to 9 per cent after scalene section. In one instance following scaleniotomy, the fever which previously had been continuously remittent, after the third day fell to normal, with a decrease in the sputum and marked subjective improvement. In the remaining cases the patients have not been under observation over a sufficient period of time to warrant final conclusions.

CONCLUSIONS

1. Phrenic block has an established place in the surgical treatment for pulmonary tuberculosis, regardless of location. This measure may be useful either independently or as an adjunct to thoracoplasty. The utilization of phrenic block as a test of the patient's recuperative power or resistance is a recognized procedure.

2. The increased respiratory activity of the upper part of the thorax after paralysis of the diaphragm raises a question as to the physiologic soundness of the operation in apical lesions.

3. From experimental and clinical studies the scaleni have been proved to have an important relation to the respiratory activity of the upper part of the thorax.

4. In a series of cases of pulmonary tuberculosis scaleniotomy has induced satisfactory immobilization of the involved apex.

5. Combined scaleniotomy and phrenic block apparently answer the need for some surgical measure to induce apical rest coincident with paralysis of the diaphragm. When phrenic block has not effected the desired improvement, scaleniotomy may be performed as an adjunct of a conservative type at a later period, before resorting to a radical measure.

6. The anatomic relationships render simple the combined operation (scaleniotomy and phrenic exeresis).

7. Alone or combined with phrenic exeresis, scaleniotomy must be considered as a preparatory stage when more radical measures are inevitable.

8. Through section of the scaleni, the first rib is subjected to the caudal pull of the intercostal muscles; therefore, when paravertebral thoracoplasty must subsequently be performed, the extent of the resection of the first rib may be reduced and the desired effect obtained. Hence the technical difficulties in the surgical approach to this portion of the first stage of the thoracoplasty may be materially reduced.¹⁶

16. Since the manuscript of this paper was submitted, two articles have appeared in the continental literature closely paralleling our work and results, namely: H. Els (*Zentralbl. f. Chir.* **57**:2228 [Sept. 6] 1930) and Koch, Els and Junkersdorf (*Beitr. z. Klin. d. Tuberk.* **75**:772 [Oct. 3] 1930).

ACUTE PANCREATITIS (PANCREATIC NECROSIS)

AN EXPERIMENTAL AND CLINICAL STUDY, WITH SPECIAL REFERENCE
TO THE SIGNIFICANCE OF THE BILIARY TRACT FACTOR *

OWEN H. WANGENSTEEN, M.D.

N. L. LEVEN, M.D.

AND

M. H. MANSON, M.D.

MINNEAPOLIS

The consistent frequency with which gallstones or disease of the gallbladder have been found in association with acute pancreatitis has served to confirm the belief that biliary infection predisposes to pancreatitis. Fitz, who recognized acute pancreatitis as a disease entity, was cognizant of a probable causative relationship between disease of the gallbladder and pancreatitis.

In 1907, Egdahl found that gallstones were present in 42 per cent of 107 reported cases. In a recent statistical study, Schmieden and Sebening found that gallstones were present in 69.8 per cent of a series of 1,278 cases of acute pancreatitis collected from 104 German surgical clinics, from 1919 to 1927. That disease may be present in the gallbladder in the absence of gallstones in no small number of cases is evidenced by the number of instances in which cholecystectomy is performed in the absence of cholelithiasis. In 1919, W. J. Mayo stated that infected gallbladders and usually stones were present in 90 per cent of all cases of acute and chronic diseases of the pancreas in which operation was performed at the Mayo Clinic. It is significant, too, that in Schmieden and Sebening's report, 65 per cent of the total number of instances of acute pancreatitis occurred in women, whereas a number of previous smaller statistical studies have shown a predominance in men. The latter observation is in agreement with the greater incidence of disease of the gallbladder in women.

The importance of this frequent association is further emphasized by the fact that two commonly discussed etiologic factors of acute pancreatitis seek their explanation in a coexisting disease of the biliary

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* From the Department of Surgery of the University of Minnesota.

* Acute pancreatitis and acute pancreatic necrosis have been used interchangeably in this paper. The term pancreatitis is so well established in the literature that it would appear futile to substitute the more accurately descriptive designation of pancreatic necrosis.

tract. The acceptance of the reflux of bile as an etiologic agent in acute pancreatitis centers about the observation of Opie that a gallstone lodged at the ampulla of Vater may convert the choledochus and duct of Wirsung into a common channel and permit the retrojection of bile into the pancreatic duct. Since Opie's report in 1901, a large number of similar observations have been recorded. The experimental production of acute pancreatitis by the injection of bile into the pancreatic duct by many investigators has served to confirm the significance of Opie's observation.

Serious consideration of the lymphatic factor as an etiologic agent of acute pancreatitis dates from the experimental work of Maugeret in 1908. Though failing to effect an acute pancreatitis by producing a chemical cholecystitis in the dog following the introduction of formaldehyde and charcoal into the gallbladder, Maugeret believed that the swelling and interstitial edema of the gland demonstrated that infection may be propagated to the pancreas from the biliary passages by the lymphatic route.

This suggestion soon found corroboration in the clinical observations of Arnsberger, viz., that evidence of pancreatic injury may obtain in acute infections of the biliary tract. In this country, Deaver in particular has championed the belief that acute pancreatitis results through the spread of infection from the gallbladder to the pancreas by way of the lymphatics. Now, it is endorsed by many, and appears to have found substantial support in the experiments of Graham and Peterman.

Recently, however, Kaufmann¹ stated that no experimental or clinical proof exists for the origin of acute pancreatitis through the medium of lymphangitis extending from infection in the gallbladder. In their monograph on "Diseases of the Gall Bladder and Bile Ducts" (1928), Graham and his associates stated that "we were probably in error in our former conclusion that we had demonstrated a lymphogenous origin of pancreatitis from a cholecystitis." The virtual abandonment of the bile factor as an etiologic agent in the genesis of acute pancreatitis by Mann and Giordano² has dealt a severe blow to the other factor that made special recognition of a causative relation between the frequent association of disease of the gallbladder and acute pancreatitis.

Clinically, the common factor or denominator (at least, far more frequent than any other single factor) of acute pancreatitis is disease of the biliary tract. For a long time, this fact has been recognized.

1. Kaufmann, M.: *Surg. Gynec. Obst.* **44**:15, 1927.

2. Mann, F. C., and Giordano, A. G.: *Bile Factor in Pancreatitis*, *Arch. Surg.* **6**:1 (Jan.) 1923.

The mechanism through which disease of the gallbladder predisposes to pancreatitis has been in dispute. The denial of the existence of experimental proof for the genesis of pancreatitis through the reflux route as well as through a lymphatic origin necessitates a reconsideration of the relationship of disease of the biliary tract to acute pancreatitis.

THE PROBLEM OF ACUTE PANCREATITIS

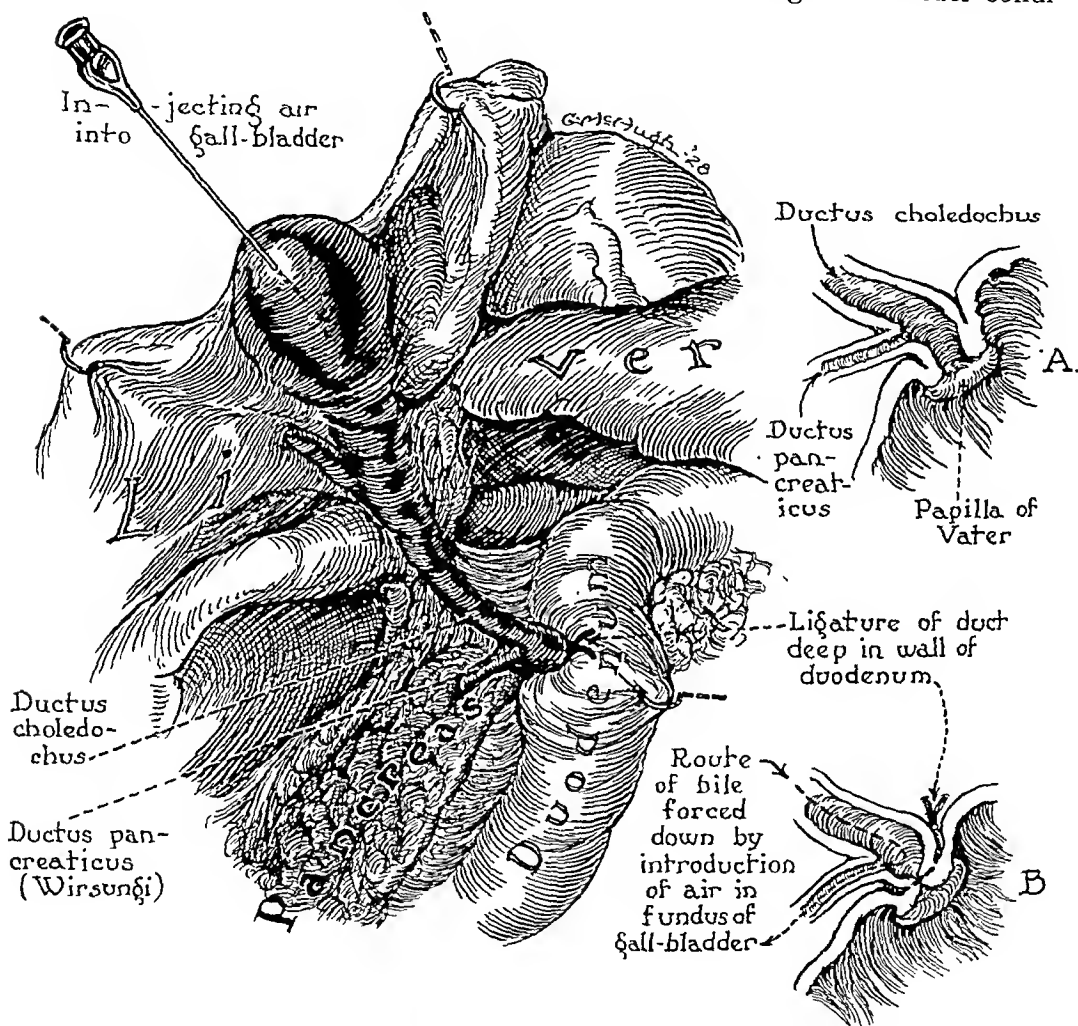
At necropsy Chirari not infrequently observed necrosis in the pancreas of patients in whom during life no symptoms of acute pancreatitis had been present, and he formulated the idea of self-digestion as the cause of pancreatitis. Postmortem necrosis of the pancreas is readily *differentiated from actual pancreatic necrosis through the lack of cellular reaction in and surrounding the areas of necrosis*. The proteolytic ferment of the pancreas, trypsinogen, is inactive in the pancreas and normally acquires the power to digest protein only when rendered active by succus entericus in the duodenum. Collection of the secretion from a pancreatic fistula has determined the accuracy of this observation for man as well as for the dog. A number of substances, however, exhibit the ability to convert trypsinogen into active trypsin. Experiment in vitro has determined that calcium salts (Delezenne), pressed liver juice and amino-acids (Wohlgemuth), as well as a number of other substances, possess this property. According to Delezenne, Fürth and Schütz, bile activates trypsinogen only when the pancreatic juice already exhibits a slight digestive action for protein, and Lattes found bacteria and leukocytes to have practically no activating influence for trypsinogen. Experiment in vivo, viz., injection into the pancreatic duct, has shown that of substances that concern the living organism, bile and duodenal content preeminently exhibit this property.

Following the injection of sterile bile or duodenal content into the pancreatic duct, acute pancreatitis almost regularly ensues. Polya found that the injection of 1 cc. of active trypsin into the pancreatic duct resulted in acute pancreatitis, whereas the injection of inactive substances such as inactivated trypsinogen, physiologic solution of sodium chloride or blood serum, even to the extent of rupture of the ducts, failed to produce the disease.

Rosenbach produced hemorrhages in the frog's tongue following the lingual injection of active trypsin, and Kirchheim and Matthes observed local hemorrhage and edema following the injection of trypsin into the vein of the ear of a rabbit, as well as hemorrhages and edema in the lungs. Trypsin, then, apparently possesses the property of digesting living tissue. Camus and Gley have been able to collect active trypsin from the pancreatic duct under the influence of stimulation of the vagus.

The presence of active trypsin in the pancreatic ducts alone, however, does not appear to be sufficient criterion for the production of the disease.

The study of the problem of acute pancreatitis, therefore, resolves itself into a consideration of how the pancreatic ferment may become activated within the gland so as to permit of self-digestion under condi-



A. Cross section: relation of duct of Wirsunği to common duct and papilla of Vater
 B. " " " " ducts with papilla of Vater tied off

Fig. 1.—Establishment of a common channel of the common bile and pancreatic ducts by placement of a ligature at the ampulla. Overdistention of the gallbladder with air causes contraction and emptying of the gallbladder with projection of bile into the pancreatic duct. An intravesical pressure in the gallbladder of 60 mm. of mercury is necessary to effect evacuation, but retrojection of bile into the pancreatic duct from the choledochus occurs at pressures physiologic for the biliary tract (from 210 to 240 mm. of pressure of bile in the common duct).

tions that come within the scope of functional or anatomic alterations in the human organism. In this report, we have been concerned primarily with an investigation of the rejected bile and lymphatic factors.

METHOD OF STUDY

These experiments, extending over five years, were done almost entirely on cats. Two hundred and eighty-nine animals were used; only ten dogs were used, and only in those experiments concerned with the effect of trauma in the genesis of pancreatitis. The cat is favorable for the investigation of the biliary reflux factor, in that the major pancreatic duct empties into the terminal end of the choledochus. By careful incision of the duodenal wall over the terminal end of the common bile duct, an extramucosal exposure of this point of union is easily made, and a ligature placed distally converts the two into a common channel. When this study was first commenced we were interested in determining whether normal bile projected into the pancreatic duct under the influence of the contraction of the gallbladder would give rise to an acute

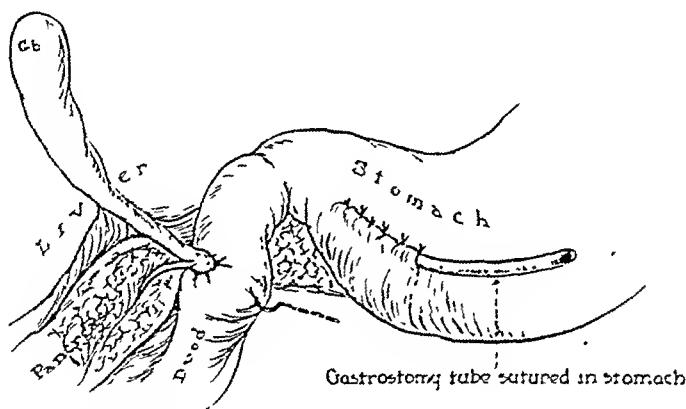


Fig. 2.—Establishment of a common channel of the common bile and pancreatic ducts with a gastrostomy tube in the stomach for feeding. A high incidence of pancreatitis was obtained by feedings of milk, cream and olive oil (fifteen of thirty-one, or 48.7 per cent). After excision of the gallbladder, this incidence was reduced (three out of eleven, 27.2 per cent) with feedings of fat, but was still higher than when dextrose, alcohol or protein were fed with the gallbladder in situ.

pancreatitis. The ejection of bile from the gallbladder was effected by overdistingending this viscus by the introduction of air into the fundus with a fine hypodermic needle and a syringe. Following overdistingention of the gallbladder, the latter contracted, and droplets of bile and air together passed over into the pancreatic duct, usually only into the beginning of the pancreatic duct, but occasionally well into the duct in the midportion or tail of the gland. In a few cats, methylene blue (methylthionin chloride, U. S. P.) was injected into the gallbladder instead of air, and the pressure at which the methylene blue-stained bile was regurgitated into the pancreatic duct was ascertained as well as the pressure necessary to effect an emptying of the gallbladder.

A number of experiments were also performed in which a common channel was established by placing a ligature at the ampulla, but without introducing anything into the biliary duct system. A gastrostomy of the Witzel type was done in these cats, and frequent feedings of milk, cream and olive oil and bile salts were given through the gastrostomy tube to effect a contraction of the gallbladder. The effect of feedings of dextrose, alcohol and a diet high in protein through a gastrostomy tube in cats with a common channel of biliary and pancreatic duct was studied. In another series of cats, fatty meals were administered through the tube after excision of the gallbladder.

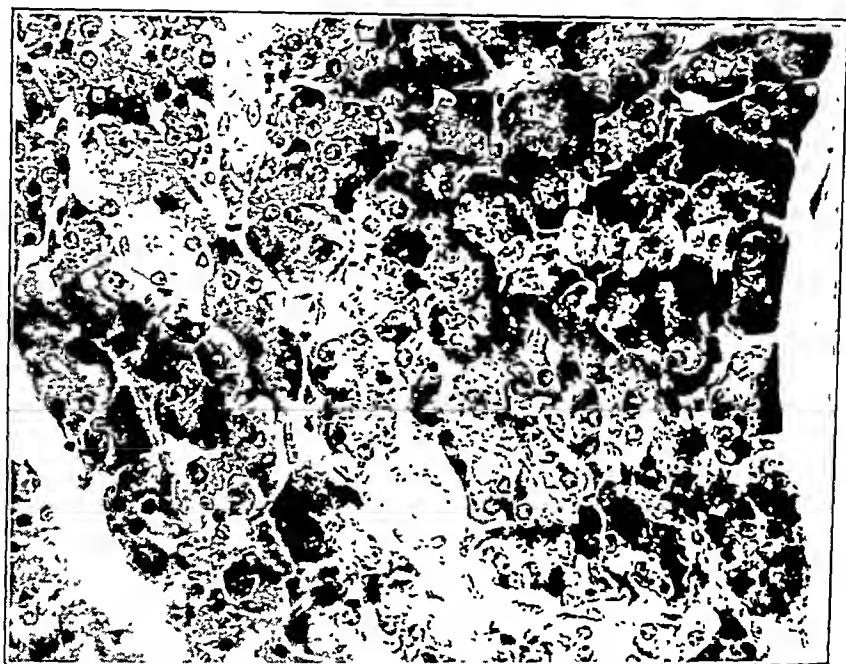


Fig. 3.—Normal pancreas of a cat; $\times 250$.

In several cats, infection was established in the biliary passages by making an anastomosis between the stomach and the gallbladder. Cholecystitis and cholangitis were almost constant accompaniments following cholecystogastrostomy. In some of these experiments, the major pancreatic duct also was tied. In a number of other cats, bacteria and gauze or unsterile human gallstones and gauze were placed in the gallbladder. Ligation of the major pancreatic duct was also performed in a few of these procedures. In these experiments, we were anxious to determine whether the establishment of acute infection in the biliary tract would result in acute pancreatitis. In a few instances, bacteria were injected directly into the substance of the pancreatic gland.

The influence of a combination of factors which were ineffective in producing pancreatic necrosis when operating as single factors was also ascertained, such as ligations of the pancreatic duct plus the subcutaneous



Fig. 4.—Fat necrosis of the omentum with leukocytic wall after the projection of bile into the pancreatic duct consequent on overdistention of the gallbladder in the presence of a common channel of the common bile and pancreatic duct; $\times 250$.

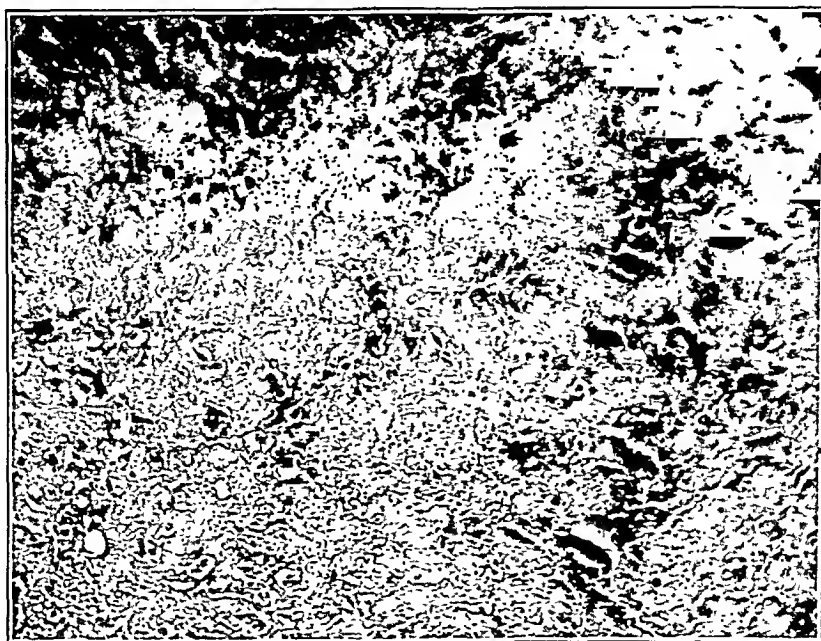


Fig. 5.—Pancreatic necrosis after the same procedure as in figure 4. The loss of contour of pancreatic acini with dissolution of the pancreatic substance is well shown; $\times 100$.

administration of pilocarpine in physiologic doses; injections directly into the pancreatic substance plus ligations of the pancreatic duct or chemical stimulation of the vagus with pilocarpine.

In several cats and dogs, trauma to the pancreas was caused by complete division of the gland, division of the major ducts or crushing of the gland with a crushing clamp.

All experiments were done under ether anesthesia with aseptic technic. In the animals that died, necropsy was performed, usually directly following the death of the animals; a number were killed when it was apparent that death was imminent. In each experiment the pancreas was examined grossly and microscopically for evidence of pancreatic necrosis. Blocks of pancreatic tissue were embedded in paraffin and the sections were stained with hematoxylin and eosin.

SUMMARY OF RESULTS

The outcome of the experiments appears in the accompanying tables, and will not be described in detail. All the gross criteria of pancreatic necrosis, viz., hemorrhage in the pancreas, subperitoneal fat necrosis and free fluid in the peritoneal cavity did not occur in many instances. In four of the thirteen instances in which a common channel of pancreatic and common bile ducts was established and retrojection of bile obtained into the pancreas under the influence of contraction of the gallbladder brought about by overdistinging this viscus with air, gross hemorrhages were apparent in the pancreas.

In one animal, death occurred about twenty minutes after the animal had fully recovered from the anesthesia or about an hour after completion of the operation. In this instance, bile could be seen in the tail of the pancreas, and small hemorrhages were present throughout the gland. No fat necroses, however, were apparent,³ but microscopic evidence of necrosis in the peripancreatic fat was present.

In two of these, the pancreas was fiery red throughout its greater portion. Hemorrhagic fluid in the peritoneal cavity was present in one of these cats. Gross hemorrhages were also seen in the instances in which active tryptic ferment was injected into the pancreatic duct as well as after the direct injection of bile into the pancreatic duct. In the majority of the experiments, therefore, the single gross evidence of pancreatic necrosis present was fat necrosis over the pancreas. In each instance, however, the pancreas was examined microscopically with extreme care, to make certain that microscopic evidence of actual

3. Following the production of acute pancreatic necrosis in dogs, Seidel found that fat necroses were present only when the period of survival was more than twelve hours.

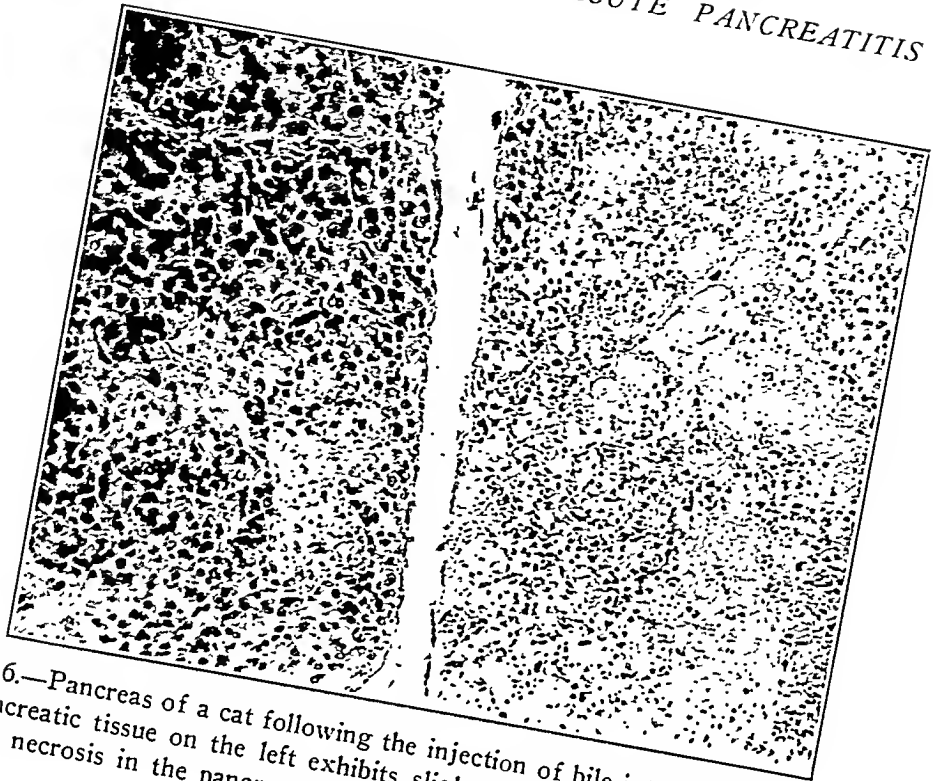


Fig. 6.—Pancreas of a cat following the injection of bile into the pancreatic duct. The pancreatic tissue on the left exhibits slight injury, whereas the cellular reaction and necrosis in the pancreas on the right side is far greater; $\times 100$.

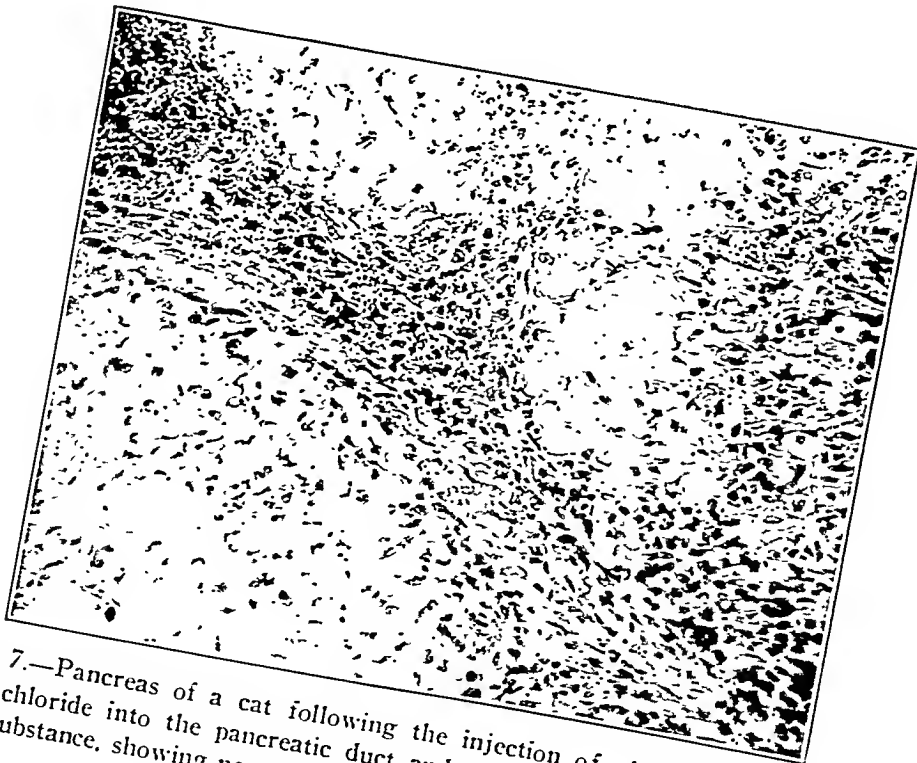


Fig. 7.—Pancreas of a cat following the injection of physiologic solution of sodium chloride into the pancreatic duct and the injection of bile into the pancreatic substance, showing necrosis, hemorrhage and leukocytic infiltration; $\times 100$.

pancreatic necrosis was present. The necessity for differentiating post-mortem autolysis from pancreatic necrosis has been referred to, and in each instance in which fat necroses over the pancreas were observed grossly and no microscopic cellular reaction was found in the pancreas

TABLE 1.—*Establishment of a Common Channel of Bile and Pancreatic Ducts by Ligature at Ampulla*

Type of Operation	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
1. Simple ligature at ampulla.....	7	1	1
2. With injection of air.....	13	8	8
3. With infection of gallbladder with agar streptococci and gauze	4	3*	1
4. Common channel plus gastrostomy and feedings of cream, olive oil and bile salts.....	31	18	15
5. Same as 4 but feedings of dextrose.....	9	2	2
6. Same as 4 but feedings of alcohol.....	9	2	2
7. Same as 4 but feedings of protein.....	13	0	0
8. Same as 4 but with excision of gallbladder....	11	3	3
9. Same as 4 plus infection of gallbladder.....	19	5	5
10. Same as 4 plus daily subcutaneous injections of 1 mg. of pilocarpine hydrochloric acid....	6	6	3
11. Same as 4 plus injection of iodized oil into gallbladder	6	3	1†
12. Same as 4 plus injection of 2 cc. of pancreatic extract into gallbladder.....	3	1	1

* Two were postmortem necroses.

† No roentgen evidence of reflux into pancreatic ducts.

TABLE 2.—*Injection into Pancreatic Duct Followed by Duct Ligation*

Fluid Injected	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
1. Bile.....	5	5	5
2. Pancreatin.....	3	3	3
3. Saline.....	13	3	1

TABLE 3.—*Ligation of Major Pancreatic Duct*

Type of Operation	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
1. Ligation of major pancreatic duct.....	6	0	0
2. Same as 1, plus daily subcutaneous injection of pilocarpine hydrochloric acid, 1 mg.	6	3	3
3. Same as 1, plus infection of gallbladder.....	13	3	2
4. Same as 1, plus infection of gallbladder plus gastrostomy and feeding of fat.....	4	2	1

or in the gross areas of fat necroses themselves, the result has been counted as negative.

Injection of bile into the pancreatic duct terminated similarly in the five experiments in which this procedure was practiced (table 2). In one cat, the injection of physiologic solution of sodium chloride into the pancreatic duct, followed by its ligation, terminated in the death of the animal (table 3). Scattered fat necrosis and microscopic evidence

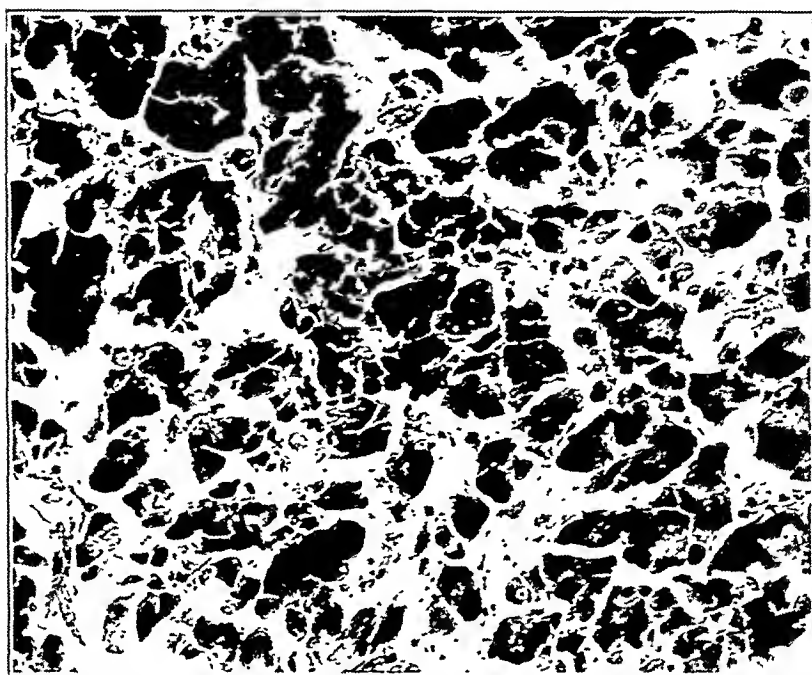


Fig. 8.—Interstitial edema of the pancreas after the injection of bacteria into the gland. A similar type of reaction may be seen following infection of the gall-bladder; $\times 250$.

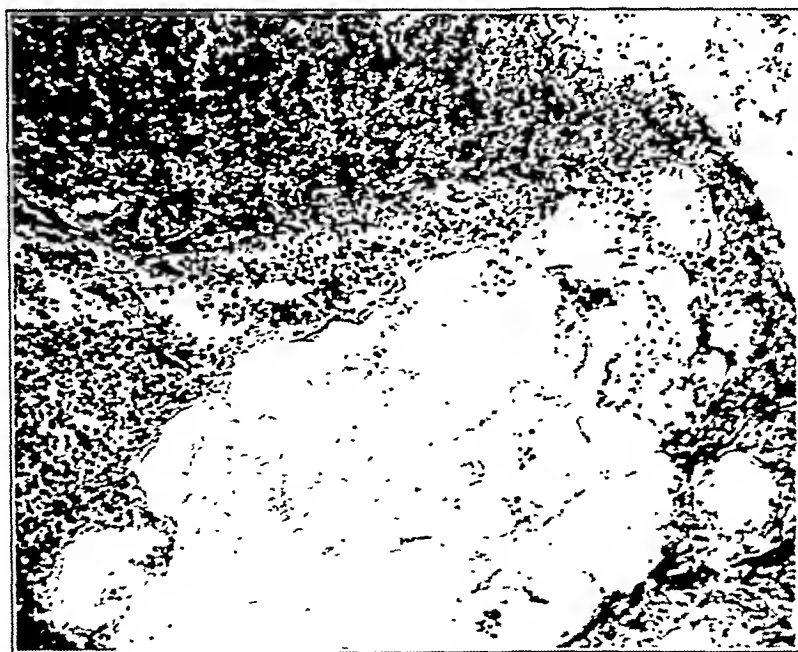


Fig. 9.—Necrosis in the pancreas of a cat and marked cellular reaction following ligation of the major pancreatic duct and daily subcutaneous administration of pilocarpine; $\times 100$.

of damage to the pancreas were present in this instance. Attending the isolation of the duct, however, considerable trauma had occurred to the gland. Similar injections of the solution into other animals failed to produce acute pancreatitis.

Following cholecystogastrostomy, infection of the gallbladder regularly followed, and cholangitis with abscesses of the liver was occasionally observed. The presence of intestinal worms in the gallbladder following such an anastomosis was not an infrequent observation. Although acute infection of the peritoneum occurred not infrequently, following the establishment of acute infection in the biliary passages by this method or after the introduction of septic foreign bodies into

TABLE 4.—*Infections of Gallbladder*

Type of Operation	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
1. Simple infection of gallbladder.....	18	1*	1*
2. Same as 1, plus pilocarpine, 1 mg. subcutaneously	8	0	0
3. Same as 1, plus gastrostomy and feeding of fat	9	1	0
4. Same as 1, plus gastrostomy plus pilocarpine subcutaneously	3	0	0
5. Same as 1, plus ligature at ampulla (see table 1, no. 3).....	4	3	1
6. Same as 1, plus ligature at ampulla, plus gastrostomy and feeding of fat (see table 1, no. 5)	19	5	5
7. Same as 1, plus ligature of pancreatic duct (see table 3, nos. 3 and 4).....	13	3	2
8. Same as 7, plus gastrostomy and feeding of fat (see table 3, no. 4).....	4	2	1
9. Cholecystogastrostomy	5	0	0
10. Same as 9, plus ligation of major pancreatic duct	6	2	0

* In this animal bile was grossly evident in pancreatic ducts, a demonstration of the possibility of reflux in the absence of mechanical block at the ampulla.

the gallbladder, only once was positive evidence of pancreatitis obtained, and in this instance bile was seen in the pancreatic ducts despite the absence of organic obstruction at the ampulla. When the major pancreatic duct was ligated, in addition to the establishment of the biliary infection, definite evidence of pancreatic injury was obtained in a few instances (table 4). Not uncommon observations following the establishment of biliary infection were a loss of definite contour of the pancreatic acini, with an edema or swelling of the interstitium. Hemorrhage, pancreatic necrosis or fat necrosis with microscopic cellular reactions, however, were not seen.

In one instance, following the direct injection of bacteria into the gland, definite microscopic evidence of necrosis was present thirty days later. However, when the animal was killed it was found to be in

good health, and no gross evidence of acute pancreatitis was present at autopsy. In one dog in which biopsy was done on the pancreas a little more than two hours after the injection of bile into the substance of the gland, the pancreas appeared hemorrhagic, and definite microscopic evidence of necrosis of the gland was present. In another dog, though the animal survived and no marked gross alteration in the gland was seen, microscopic examination demonstrated acinar destruction.

Though death of the animal not infrequently followed pancreatic division or crushing, a definite acute pancreatitis occurred only once. The escape of pancreatic juice into the peritoneal cavity in the presence

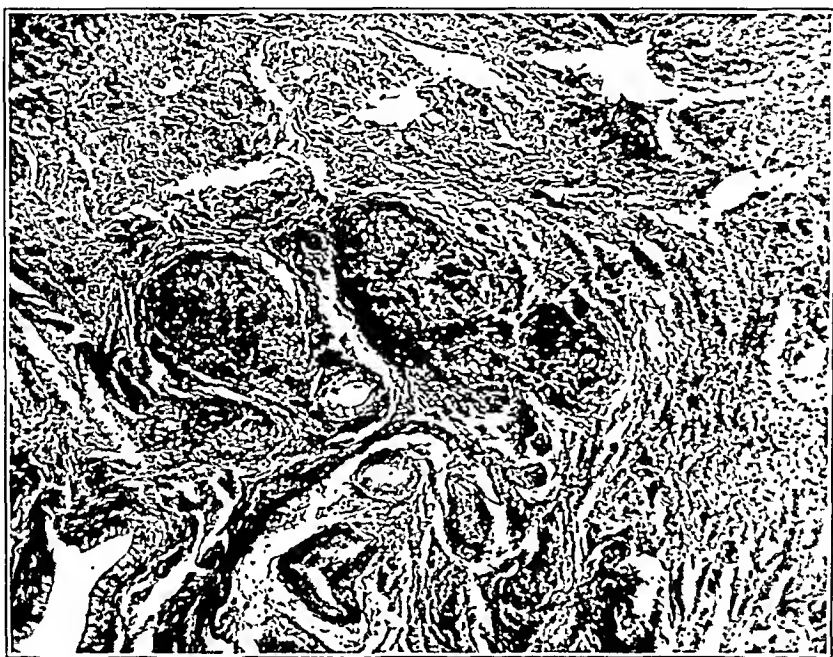


Fig. 10.—Fibrosis of the pancreas after crushing with a Payr clamp; $\times 100$.

of the trauma incident to operation did, as one should expect, frequently result in the death of the animal. In such instances, fat necroses were often present, but the pancreatic gland itself remained normal.

COMMENT

In the procedures in which acute pancreatitis followed the injection of bile into the pancreatic duct, or its retrojection under the influence of contraction of the gallbladder, the time factor required for the production of the disease requires comment. It need scarcely be mentioned that the death of the animal following the establishment of a common channel of bile and pancreatic ducts does not signify a positive result. That small animals, such as the cat, survive occlusion of the common bile duct for only a short time is well known.

It was noted, however, that even though pancreatic necrosis occurred in all five instances in which bile was injected into the major pancreatic duct, followed by ligation of the duct, the period of survival was longer than in the animals in which the acute pancreatitis was produced by overdistention, and the subsequent contraction of the gallbladder, in the presence of a common channel. Undoubtedly, the absence of obstruction to the choledochus, when the injection is made directly into the pancreatic duct, permits of a longer survival.

The establishment of a common channel alone by ligation beyond the point of juncture of the two ducts was followed by a positive result

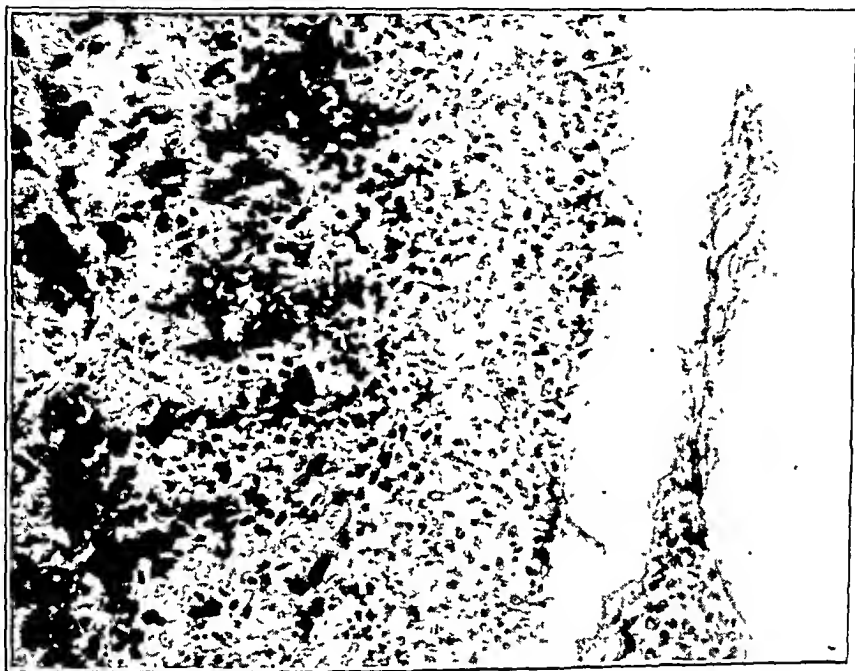


Fig. 11.—Necrosis of the pancreas with cellular reaction following the establishment of a common channel of the common bile and pancreatic ducts by placement of a ligature at the ampulla and feeding of fatty meals through a gastrostomy tube; $\times 100$.

only once in the seven instances in which this procedure was done. In the thirteen experiments in which an emptying of the gallbladder was effected by the injection of air into the gallbladder, a positive result was noted eight times. In five other cats, the pressure at which the regurgitation occurred was ascertained by inserting a needle into the common bile duct just proximal to the ligature at the ampulla, but distal to the point of juncture of the pancreatic and bile ducts. A water manometer was employed to measure the pressure. Methylene blue instead of air was then introduced into the gallbladder with a 20 cc. Luer syringe through a needle puncture in the fundus of the gallbladder.

The tension in the gallbladder was measured with a mercury manometer. The pressure necessary to effect a contraction and emptying of the gallbladder was surprisingly great. The lowest intravesical pressure at which emptying of the gallbladder occurred under the influence of overdistention was 60 mm. of mercury; in one instance, a pressure of 80 mm. of mercury was necessary to effect contraction and emptying. However, regurgitation of bile from the common bile duct into the pancreatic duct occurred at much lower pressures. In one instance, slight regurgitation occurred at a pressure of 190 mm. of water. In the other experiments, regurgitation began at a pressure of from 210 to 240 mm. of water. Following contraction of the gallbladder, the pressures in the common bile duct rose suddenly to from 350 to 570 mm. of water and occasionally to as high as 800 mm. At pressures of from 350 to 570 mm. of water in the common bile duct, regurgitation into the pancreatic duct was regularly observed.

Later, however, we found that pancreatic necrosis could be produced with a fair degree of regularity by effecting a contraction of the gallbladder under the influence of a fatty meal of cream and olive oil fed through an opening produced by gastrostomy.⁴ In the thirty-one instances in which this operation was done, positive evidence of pancreatic necrosis was obtained fifteen times. The rarity with which evidence of pancreatic necrosis was observed following simple establishment of a common channel of the bile and pancreatic ducts by placing a ligature at the ampulla (once in seven experiments) and its more frequent occurrence (fifteen times in thirty-one experiments) when fatty meals were added by feeding through a gastrostomy tube bespeaks the significance of the easier activation of the pancreatic ferment at the height of digestion. That the contraction of the gallbladder under the influence of the fatty meal may in part have been responsible for this increased frequency with which pancreatitis occurred following the establishment of a common channel of bile and pancreatic ducts, although no roentgen evidence of the regurgitation of bile from the gallbladder into the pancreatic ducts was obtained following preliminary injections of iodized oil into the gallbladder, is indicated by the lessened incidence of pancreatic necrosis after the excision of the gallbladder (three of eleven cats). Also, feedings of dextrose or alcohol failed to cause pancreatic necrosis with as great regularity as a fat diet. In thirteen cats in which a common channel was established, the feeding of protein failed to produce pancreatitis in a single instance. Hillyard⁵ has indicated that feeding of the protein increases the secretion of bile more than any

4. Leven and Wangenstein: *Proc. Soc. Exper. Biol. & Med.* **27**:965, 1930.

5. Hillyard: *Proc. Staff Meet. Mayo Clin.* **5**:127, 1930.

other type of food. The series of cats fed fatty meals has been augmented to thirty-one animals, through the performance of experiments on three series which together equal in number those fed on a carbohydrate diet, in order to make certain that the incidence of pancreatitis after the feeding of fat occurred uniformly with such regularity.

The frequency with which this occurrence was observed after the feeding of fatty meals together with its lessened frequency after excision of the gallbladder serves to emphasize the significance of the contraction of the gallbladder for the development of pancreatitis in the presence of a common channel of pancreatic and common bile ducts. Though

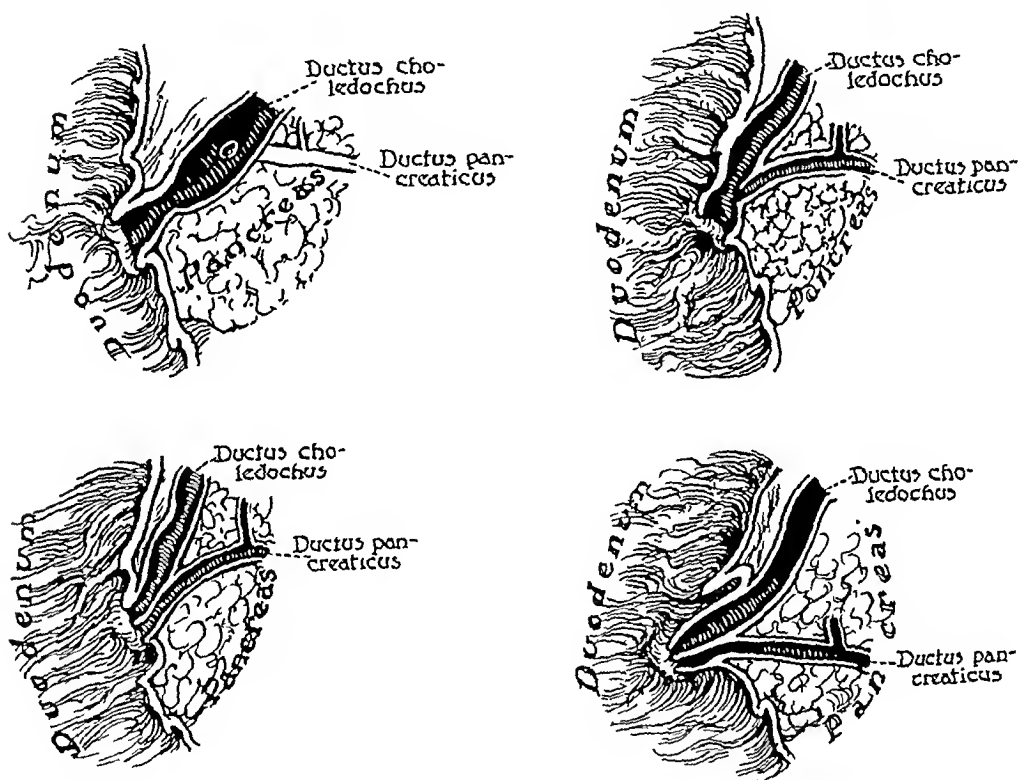


Fig. 12.—Drawings of usual types of union of common bile and pancreatic ducts in man (from Corning).

the factor of more effective activation by bile of the tryptic ferment of the pancreas in animals fed on a fat diet is not excluded, it appears unlikely that the latter possibility is of any moment, especially as when feedings of fatty meals through a gastrostomy tube were given to animals with infection of the gallbladder (table 4, no. 3) negative results were obtained in all of nine trials.

Reflux of Bile.—That the mechanism of the regurgitation of bile into the pancreatic duct, through the agency of a gallstone impacted in the ampulla, accounts for only a minority of cases of acute pancreatitis, needs no emphasis. In an inquiry made by Guleke in 1924, on 437 cases

of acute pancreatitis collected from 38 German surgical clinics, calculous obstruction at the ampulla was present in only 1.4 per cent of the total number. In Schmieden and Sebening's larger and more recent statistical study of 1,278 cases, 4.4 per cent exhibited a gallstone at the papilla. Stones were present in the common bile duct in 5 per cent of Guleke's cases, and in 13.6 per cent in Schmieden and Sebening's cases. Even when cognizance is taken of the fact that the obstructing calculus may have slipped back into the common duct or may have been extruded into the duodenum (Williams and Busch, Zoepffel and others), it is apparent that the reflux of bile through such an agency accounts for only a small proportion of cases of acute pancreatitis.

In their study, Mann and Giordano found that the anatomic possibility for a reflux of bile into the pancreatic duct obtained in only 3.5 per cent of 200 cadavers. Most anatomic investigations have shown that a common ampullary termination of the choledochus and major pancreatic duct occurs in the majority of instances. Opie found such a communication in 89 of 100 cadavers; Baldwin observed a common ampulla in 70 of 90 dissections (78 per cent), and in 32 of 43 specimens examined by Ruge (75 per cent), a common termination of the two ducts existed.

Opie recognized that the possibility for a reflux of bile did not obtain in each instance in which an ampulla was present, but believed that such a regurgitation could occur in about one third of the cases. By injecting a dye opaque to the roentgen rays directly into the distal portion of the pancreatic duct, in the tail of the gland, Schmieden and Sebening found that a filling of the choledochus occurred in 8 of 35 instances (22.8 per cent).

We should like to refer to the experiments of Cameron and Noble,⁶ reported from this laboratory with reference to the possibility of such a reflux. They introduced a small biliary calculus, 3 mm. in diameter, into the hepatic duct of 100 fresh necropsy specimens, and pushed the calculus into the terminal portion of the choledochus. The hepatic duct was then connected with a reservoir of water and a manometer, and water was forced into the hepatic duct at a pressure of about 100 mm. of water. In 66 instances, a reflux of bile occurred into the pancreatic duct. In 74 of the 100 instances, an ampullary communication was present; in 8 of these, the duodenal orifice was so large that the calculus was extruded into the duodenum. It is evident, therefore, that the anatomic possibility for this reflux obtains with far greater frequency than the measurements made by Mann and Giordano on specimens fixed in formaldehyde would indicate.

6. Cameron, A. L., and Noble, J. F.: Reflex of Bile up the Duct of Wirsung Caused by an Impacted Biliary Calculus, *J. A. M. A.* **82**:1410 (May 3) 1924.

Archibald has adequately demonstrated for the cat that the sphincter of Oddi can withstand pressures that would permit the regurgitation of bile into the pancreatic duct, in the absence of organic obstruction at the ampulla. Mann and Giordano, however, were unable to produce pancreatitis when bile was run into the pancreatic duct under gravity pressure, at pressures physiologic for the biliary tract.

Mann and Giordano found that the intraductal pressure in the choledochus of the dog rarely exceeded a pressure of 350 mm. of bile. Bile is secreted continuously, whereas pancreatic juice is secreted intermittently, but at pressures similar to those in the biliary tract, according to Mann and Giordano. In unanesthetized dogs during digestion, Harms, of Guleke's clinic in Jena, has recently reported higher pressures in the pancreatic duct than in the common bile duct. This observation, Guleke believes, is further evidence against the reflux of bile as a frequent etiologic factor of acute pancreatitis. Although the onset of acute pancreatitis not infrequently follows fairly directly the ingestion of an unusually large meal, bile cannot be regurgitated into the pancreatic duct under normal circumstances; if that were possible, many of us would live in constant dread of this potential danger. Mann and Giordano have shown, however, that during retching or vomiting, the pressure in the choledochus may attain 1,000 mm. of bile.

Westphal was able to demonstrate in several laboratory animals that electrical stimulation of the vagus or of the sympathetic causes disturbances in the tone of the gallbladder and its ducts, as well as in the sphincter of Oddi. Such changes were also elicited following the administration of drugs that influence the sympathetic or parasympathetic nerves. Disturbances in the contractile tone of the biliary ducts and ampullary sphincter mechanism have been called into question by Westphal as the stasis factor contributing to the formation of gallstones. This opinion is shared by Aschoff and has also received the approbation of others. Rost expressed the belief that in many instances of icterus without demonstrable mechanical obstruction a disturbance in the sphincteric arrangement at the terminal end of the common bile duct may be responsible.

Giordano and Mann⁷ recently found a thickening of the terminal end of the common bile duct, with an increase in muscle tissue in some instances of duodenal ulcer and cholecystitis. They suggested that this thickening may cause loss of function or spasm. In the latter event, however, they are of the belief that both the pancreatic and common bile ducts would be occluded.

7. Giordano, A. S., and Mann, F. C.: Sphincter of Choledochus, *Arch. Path.* 4:493 (Dec.) 1927.

That an imbalance in the musculonervous control at the ampulla might operate to effect a regurgitation of bile into the pancreatic duct is easily understandable. That regurgitation of bile actually occurs through such an agency, however, remains to be demonstrated.

Archibald's production of a regurgitation of bile in the cat concerns acute experiments under artificial circumstances. We have been unsuccessful in many attempts to effect such a regurgitation in the cat in the absence of a mechanical block at the ampulla. In one instance, however, following the establishment of infection in the gallbladder, regurgitation occurred without the existence of an obstruction at the ampulla (table 4, footnote).

The more frequent regularity with which pancreatic necrosis may be produced by injections of bile, duodenal content or other substances into the pancreatic duct, at the height of digestion, has been noted by many investigators. It has already been pointed out that acute pancreatitis is found to have its onset directly following a large meal, and often a fatty meal, and the increased frequency with which pancreatitis was produced in the presence of a common channel of pancreatic and common bile ducts when fat was fed and the decreased incidence after excision of the gallbladder lend credible support to the contraction of the gallbladder as being the significant factor rather than the performance of the experiments at the height of digestion. It is well known that patients with disease of the gallbladder are usually intolerant of fatty foods.

It has already been indicated that trypsin has the power to digest living tissue. In connection with the consideration of the biliary factor, it should also be recalled that Tatum⁸ was able to demonstrate a marked cytolytic activity for bile on tissue by immersing small blocks of various tissues in bile at body temperatures. Sellards⁹ observed local necrosis following the injection of bile into the salivary glands, and Binet has made the same observation for bile introduced subcutaneously. Following the direct injection of bile into the pancreas, we noted microscopic necrosis and hemorrhage in the gland. This activity of bile, combined with the injury to the smaller ducts in the pancreas attending ampullary occlusion, is undoubtedly a factor that aids the dissemination of the activated pancreatic ferment throughout the gland, resulting in its digestion when bile is retrojected into the pancreatic duct.

In connection with the factor of the reflux of bile as a causative agent of acute pancreatitis, the possibility of an ascending infection from the duodenum should be mentioned. It has been adequately demonstrated that the injection of duodenal content into the pancreatic

8. Tatum: *J. Biol. Chem.* **27**:243, 1916.

9. Sellards: *Bull. Johns Hopkins Hosp.* **19**:268, 1908.

duct may cause acute pancreatitis. Although Seidel has shown that the establishment of duodenal obstruction in the dog may permit the regurgitation of duodenal content into one of the pancreatic ducts, the origin of acute pancreatitis in man, through such an agency, is undoubtedly an uncommon event, even though the duct of Santorini opens into the duodenum without a sphincteric closure mechanism. Williams and Busch found that the discharge of a gallstone through the ampulla of Vater left the latter patulous, so that the possibility for regurgitation of duodenal content into the pancreatic duct was present. The occasional occurrence of acute pancreatitis in the presence of a duodenal diverticulum in juxtaposition to the terminal end of the common bile duct may have its explanation in such an origin. The migration of an intestinal parasite, especially the ascaris, through the duodenal ampulla into the pancreatic duct, is not so unusual. Schmieden and Sebening stated that about fifty such instances are to be found reported in the literature.

Lymphatic Factor.—As concerns the lymphatic factor, it is important that pancreatic necrosis did not once follow the establishment of acute infection in the biliary tract. Neither did we cause pancreatic necrosis by the direct injection of bacteria into the pancreas. Polya made injections of bacteria into the pancreatic duct in twelve dogs, and only once succeeded in producing an acute hemorrhagic pancreatitis. Interstitial inflammation or abscesses not infrequently resulted.

The frequency with which acute pancreatitis follows on a so-called "acute gallbladder attack" is well known. Many patients suffering from acute pancreatitis state that in its onset such an attack has been indistinguishable from previous similar attacks of disease of the gallbladder. However, when such patients come to operation, an acute inflammation in the gallbladder is usually not found, even though it may obviously be diseased and contain stones. In hyperacute cholecystitis, such as occurs in phlegmonous or gangrenous inflammations, the complication of clinical acute hemorrhagic pancreatitis is also unusual. It is in this latter type of inflammation in the biliary apparatus that one should expect to find the association of acute pancreatitis, if spread of the infection by the lymphatics played a prominent rôle in the etiology of acute pancreatitis. Lymphangitis in acute infections, especially those of a streptococcic nature, is a common occurrence, and spread of infection by this route is generally feared. The absence of this danger in chronic infections is also generally conceded.

Whereas Franke, Barthels and other earlier investigators have declared the existence of direct lymphatic communication between the biliary apparatus and the pancreas, Kodama failed to observe them.

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Kaufmann has commented on the experimental proof that the investigations of Graham and Peterman have lent to the lymphatic theory. Kaufmann found that in those instances in which bacteria were present in the pancreas following intraportal injections of bacteria or the establishment of acute infection in the gallbladder a bacteremia was also usually present. The more important consideration, however, is that isolation of bacteria from the pancreas is not synonymous with pancreatic necrosis. The crucial test is whether or not an actual pancreatic necrosis follows. It has already been indicated that though cloudy swelling was a regular observation in the gland following the establishment of acute infection in the gallbladder, pancreatic necrosis did not once follow.

In 1911, Arnsberger stated that since surgical intervention had been practiced more frequently for acute cholecystitis, edema and infiltration of the mesenteries in the upper part of the abdomen, as well as swelling and edema of the pancreas, were not infrequently to be seen. He was not certain, however, that this alteration in the pancreas concerned an actual pancreatitis, and referred to the fact that Kehr had previously designated the condition merely as pancreatic swelling. Arnsberger believed that it concerned infection going out to the pancreas from the biliary passages by way of the lymphatics, and described the condition as "lymphadenitis pancreatica."

More recently, Arnsberger reported four such cases, and described the presence of fat necrosis without demonstrable pancreatic necrosis. Zoepffel also observed instances of the same character, but expressed the belief that this glassy edema and swelling of the gland, associated with fat necrosis, were the precursors of acute hemorrhagic pancreatitis. In two of four such cases seen by Zoepffel during "acute gallbladder attacks," biopsy showed no evidence of injury to the pancreatic cells.

What Arnsberger and Zoepffel observed and described would appear to correspond with what obtains in the experimental animal following the establishment of acute infection in the biliary tract.¹⁰ Swelling and edema may obtain, but the well known picture of acute pancreatic necrosis does not occur.

Zoepffel's belief that the edema and swelling of the pancreas observed occasionally in so-called "acute gallbladder attacks" are precursors of actual hemorrhagic pancreatitis is an important consideration in the interpretation of the pathogenesis of acute pancreatitis, and cannot be

10. In a recent article entitled "Acute Edema of the Pancreas (Ann. Surg. 90:803, 1929), Archibald also called attention to these pancreatic changes, but stresses their occurrence as an accompaniment of regurgitations of bile that do not go on to pancreatic necrosis. DeWitt Stettin (Ann. Surg. 92:284, 1930) supports the contention of Zoepffel that acute edema of the pancreas is a forerunner of the more dangerous acute hemorrhagic pancreatic necrosis.

passed over lightly. If Zoeppfel's contention is correct, the frequent association and relation of disease of the gallbladder to acute pancreatitis are at once understandable.

As has been indicated, microscopic swelling and edema of the pancreas are not uncommon accompaniments of acute inflammations of the gallbladder in the experimental animal. It is clear, however, that these experimental pancreatic changes do not eventuate in acute pancreatic necrosis. A sufficient number of observations regarding the frequency of these changes of swelling and edema following acute cholecystitis have not accumulated to indicate the regularity of their occurrence as accompaniments or complications of acute biliary infection. In 115 cases of acute cholecystitis submitted to immediate operation during the acute stage by Zoeppfel, 11 showed evidence of pancreatic injury. At least this much is true: With the widely practiced conservative treatment for acute cholecystitis, even should these pancreatic changes obtain frequently, their termination in actual pancreatic necrosis must be an unusual occurrence; otherwise, death from acute pancreatitis as a complication during the course of acute cholecystitis should be a frequent observation. On the contrary, the relative safety of using conservative treatment in most cases of acute cholecystitis is well known.

The facts that the mortality in the type of case referred to by Arnsberger and Zoeppfel is very low (no mortality in the eight cases reported by them in which operation was performed), and that even in cases of acute hemorrhagic pancreatitis in which operation is performed the day of inception of the symptoms this figure approaches 50 per cent, would indicate that the two are fairly distinct entities.

The belief that acute pancreatitis is not the result of infection, and that necrosis is the primary phenomenon, that hemorrhage and inflammation are secondary to necrosis, occasioned Opie and Meakins to substitute the name pancreatic necrosis. This designation has been in general use in German medical literature for many years. The term "acute pancreatitis" is employed in German medical literature for only that group of pancreatic diseases which are thought to have an underlying inflammatory etiology.

To be certain, no strict pathologic distinction can be drawn between these forms of the disease. Hemorrhage in the gland in pancreatic necrosis is not a necessary accompaniment or a criterion of the grade of necrosis of the gland. In most cases of actual pancreatic necrosis, hemorrhages are present, but fatal instances in which no gross bleeding was present are well known. At the other extreme are those instances of pancreatic necrosis, commonly called pancreatic apoplexy, in which hemorrhage dominates the picture. The finding of bacteria in the pancreas in cases of actual hemorrhagic pancreatitis has been given as

evidence of the bacterial origin of the disease (Zoepffel, Brütt). In early instances, however, bacteria are usually not found, and Tower¹¹ found bacteria regularly in the peritoneal cavities of dogs following the fatal issue attending the pancreatic necrosis consequent on the extensive ligation of pancreatic vessels. Tower's observations would indicate that infection was a terminal event. Guleke, who speaks from a considerable experimental as well as a broad clinical experience, is also in accord with this opinion.

Acute pancreatitis of distinct inflammatory origin cannot be discussed at any length here, but it should be mentioned that acute purulent pancreatitis or abscess occasionally has its origin in infections in the biliary tract, spreading to the pancreas by way of the pancreatic duct, by extension through contiguity or by way of the lymphatics. Metastatic abscesses during the course of acute infections such as diphtheria and scarlet fever, and especially mumps, are not unknown. Following the perforation of chronic peptic ulcer of the stomach, abscesses in the gland occasionally occur. The prognosis of suppurative lesions in the pancreas, though serious, is, as many statistical studies have shown, better than in pancreatic necrosis.

Combination Factors.—When the pancreatic ducts alone are obstructed, as Eppinger has shown, an accumulation of detritus occurs in the major ducts, resulting from the injury to the epithelium of the duct. Rupture of the acinar walls and hemorrhage in the interstitium may also occur. This damming back of secretion in the gland may be an important contributing factor in the genesis of acute pancreatitis. The occlusion of one duct would naturally not effect the changes in the gland observed following obstruction to both ducts, but in the human pancreas, as Opie has shown, the lesser duct of Santorini is often functionless or practically so. Nordmann was able to produce acute pancreatitis in the dog only through the agency of infection, when the entire outflow of secretion from the gland was blocked.

Injury to the pancreas undoubtedly occurs through obstruction of the pancreatic duct, and under the influence of an activating agent for trypsinogen pancreatic necrosis may obtain. Hess claimed to have produced acute pancreatitis, following occlusion of the pancreatic ducts, when the ligation was done at the height of digestion. Nearly all other investigators are in accord, however, that ligation of the pancreatic ducts usually results in atrophy and a sclerosing process in the pancreas. Previous to the assertion of Camus and Gley that stimulation of the vagus results in the secretion of active trypsin from the pancreatic cells, Opie had already produced pancreatic necrosis in two cats following

11. Tower, L. E.: Pathologic Physiology of Experimental Gangrenous Pancreatitis, J. A. M. A. 86:1112 (April 10) 1926.

the ligation of both pancreatic ducts under the influence of chemical stimulation of the vagus with pilocarpine. More recently, Brocq and Binet were successful in three of four attempts to produce acute pancreatitis in dogs by this method.

Lattes has made the suggestion that the activation of trypsinogen is brought about by pancreatic necrosis, through whatever agent may cause necrosis of the gland. It was previously stated that Wohlgemuth found amino-acids capable of activating trypsinogen in vitro, and Lattes found pancreatic tissue itself quite potent in this respect. Whereas, theoretically, damaged pancreatic tissue may activate the tryptic ferment of the gland, experiment on the living animal demonstrates that this activation is usually insufficient to produce acute pancreatitis. Although pancreatic damage as the result of trauma, ligation of the duct or chemical or bacterial injury may rarely cause pancreatic necrosis when

TABLE 5.—*Injections into Pancreatic Gland Substances*

Material Injected	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
1. Bile	11 (3 dogs)	1* (dog)	1*
2. Saline	5	2†	0
3. Broth culture of killed typhoid bacilli.....	3 (2 dogs)	0	1 (dog)
4. Bile into pancreatic substance and saline into pancreatic duct	6	6	6
5. Bile into pancreatic substance plus daily subcutaneous injection of 1 mg. pilocarpine.....	3	3	3
6. Bile into pancreatic substance plus ligation of major pancreatic duct.....	4	2	2

* In the instance in which evidence of pancreatic necrosis occurred the animal was killed two hours, twenty minutes after the injection. All other animals survived the injection.

† Probably postmortem necrosis.

operating as single factors, it would appear that a combination of such factors may produce the disease.

When bile or bacteria were injected directly into the substance of the pancreas, microscopic evidence of pancreatic damage was obtained. All the animals survived the procedure, however, and the interstitial edema and swelling noted after the injection of bacteria into the gland and the occurrence of pancreatic necrosis and hemorrhage following the injection of bile were noted only after excision of a portion of the gland for biopsy from an animal that presented no unusual symptoms. When, however, bile was injected into the substance of the pancreas and saline through the pancreatic duct, a lethal outcome occurred in every instance (table 5, no. 4), with definite signs of pancreatic necrosis in each case. Similarly, when 1 mg. of pilocarpine was administered subcutaneously to animals into whose pancreas bile had been injected, a lethal pancreatic necrosis occurred in each instance (table 5, no. 5). When bile was injected into the pancreatic substance and the major

pancreatic duct also was occluded, two of four such animals died with pancreatic necrosis. Following trauma to the gland, necrosis of the pancreas is an uncommon occurrence. In man, rupture of the pancreas in acute pancreatic necrosis has resulted in only a few instances.

Whereas simple ligation of the major pancreatic duct alone failed to cause pancreatitis, in the six cats in which the major pancreatic duct was ligated and in which, in addition, pilocarpine was given subcutaneously, pancreatic necrosis was observed three times. The establishment of acute infection in the gallbladder and pilocarpine administered subcutaneously failed to produce the disease in eight trials. Feeding of fat through a gastrostomy tube in cats with acute infections of the gallbladder failed to bring about pancreatic necrosis in the nine cats in which this combination was tried (table 4, no. 3). Whereas *in vitro* infected bile activates

TABLE 6.—*Controls to Eliminate Trauma as a Factor*

	Number of Experiments	Positive Gross Changes	Positive Microscopic Changes
A. Operative Procedures			
1. Isolation of points of union of pancreatic and common bile ducts at ampulla without ligation with feeding through gastrostomy tube	3	0	0
2. Ligation of common bile duct proximal to junction with pancreatic duct plus gastrostomy..	9	0	0
3. Gastrostomy and feeding alone.....	3	0	0
B. Direct Trauma to Pancreas			
1. Crushing with Payr stomach clamp.....	3 (2 dogs)	1 (cat)	1
2. Transverse division of gland.....	8 (2 dogs)	1	0
3. Division of major pancreatic duct.....	4 (1 dog)	0	0

trypsinogen with greater facility than sterile bile, we failed to secure evidence that indicated that this obtained in the living animal. Sterile bile regurgitated into the pancreatic duct in the presence of a ligature at the ampulla produced pancreatic necrosis eight times out of thirteen trials in the injection experiments (table 1), and fifteen times out of thirty-one instances when feedings were added to the establishment of a common channel. In only five out of nineteen trials did pancreatic necrosis occur under the same conditions when the bile in the gallbladder was infected. Of the factors which are impotent when operating as single agents but capable of producing the disease when acting jointly with another factor, obstruction of the pancreatic ducts, chemical stimulation of the vagus with pilocarpine and the presence of bile in the substance of the pancreatic gland appear to be the most important. The regularity with which pancreatic necrosis follows the injection of bile or pancreatin into the pancreatic duct (table 2, nos. 1 and 2) again bespeaks the importance of the effective activation of trypsinogen in the production of pancreatic necrosis.

Experimental investigations concerning the vascular factor in the production of the disease have shown that acute pancreatitis rarely follows unless the gland is extensively devascularized. Ligations of vessels, accompanied by plugging of some of the pancreatic vessels with air, lycopodium powder, oil, wax or other substances results in acute pancreatic necrosis, a method, however, which has no parallel in the living organism. Beneke postulated that pancreatic necrosis may be brought about by a temporary arrest of blood supply, such as may obtain through the agency of vessel spasm. He referred to experiments performed by Blume and himself, in which pancreatic necrosis was caused by squeezing the pancreas between the hands for twenty minutes. Undoubtedly, however, trauma is also an important contributing factor in such an experiment, without which pancreatitis could not have been produced.

SUMMARY

The retrojection of bile into the pancreatic duct under the influence of contraction of the gallbladder produces pancreatic necrosis in the cat, with a fair degree of regularity. We have been able to effect this regurgitation in the cat by establishing a common channel at the ampulla accompanied by the feeding of fatty foods through a gastrostomy tube without the introduction of any substance into the duct system. In the absence of an obstruction at the ampulla, however, we have been unable to produce regurgitation of bile into the pancreatic duct. In man, reflux of bile into the pancreatic duct through the agency of a gallstone impacted at the ampulla has frequently given rise to acute pancreatitis, but this mechanism accounts for only a minority of instances of the disease. The anatomic possibility for such a reflux, however, obtains in a large percentage of persons, and it is possible that such a reflux may be conditioned through a disturbance in the sphincter-regulating mechanism at the ampulla. The actual occurrence of pancreatic necrosis through such an agency in man, however, remains to be demonstrated.

Following the establishment of acute infection in the biliary tract, cloudy swelling of the pancreas is regularly observed; an actual acute pancreatic necrosis, however, does not result. Clinically, pancreatic injury of a similar character appears to be an occasional accompaniment of acute infections of the gallbladder. That these pancreatic changes are precursors of pancreatic necrosis and eventuate in actual pancreatic necrosis proof is lacking; that in the presence of an activating influence for trypsinogen these pancreatic changes may eventuate in actual pancreatic necrosis appears to be substantiated.

The effective activation of trypsinogen would appear to be the essential factor in the production of the disease. Though pancreatic tissue and products of its disintegration may activate trypsinogen *in vitro*,

experiment on the living animal demonstrates that injury to the gland effected through ligation of the duct, infection or mechanical trauma is usually inadequate as a single factor to produce acute pancreatic necrosis.

The results of this study indicate the direction of subsequent investigations, viz., that the solution of the cause of probably a considerable number of instances of acute pancreatic necrosis is to be found in a combination of factors which when operating alone are inadequate to produce the disease.

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ASCENDING URINARY INFECTION

AN EXPERIMENTAL STUDY *

WILLIAM J. CARSON, M.D.

Instructor in Surgery, Marquette University

MILWAUKEE

The routes by which infection may travel in reaching the ureter and kidney from the bladder are: (1) regurgitation of the contents of the bladder through the ureterovesical orifice, (2) direct extension through the wall of the ureter, (3) extension of the infection by way of the lymphatics and (4) by way of the blood stream.

From the clinical standpoint, Rovsing,¹ Israel,² Stoeckel,³ Albarran,⁴ Warschauer⁵ and others believed that a stagnating urinary column due to ureteral obstruction favored the upward spread of organisms.

Rovsing¹ and Melchior⁶ concluded: (1) that experimental cystitis could not be produced in animals without retention of urine or trauma to the bladder; (2) that with retention of urine experimentally produced, pyelitis as a rule did not result, and (3) that trauma to the bladder with or without retention of urine produced pyelonephritis.

Zeit⁷ and Peterson,⁸ in 1899, transplanted the ureters into the intestinal tract in 141 dogs and found that infection of the kidney eventually took place.

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* From the Department of Preventive Medicine, A. O. Smith Corporation.

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Guyon and Albarran,⁹ in 1890, injected charcoal into the bladder of dogs and ligated the urethra. They found charcoal in the pelvis of the kidneys in forty-eight hours, and pyelonephritis in some of these animals.

Lewin¹⁰ and Lewin and Goldschmidt,¹¹ in 1893, injected milk, air or colored fluids into the bladder of rabbits with moderate intravesical pressure, and observed regurgitation of the contents of the bladder into the pelvis of the kidney.

Courtade and Albarran,¹² in 1894, using dogs, repeated Lewin and Goldschmidt's work and found that regurgitation of the bladder contents occurred; but they differed in their view as to what grade of intravesical pressure was most favorable to regurgitation. Sampson,¹³ in 1906, working with dogs, was unable to confirm Lewin's observations and concluded: "The reflex of urine from the bladder into the ureter may be considered an etiological factor in the causation and maintenance of renal infection only when the intravesical portion of the ureter is diseased, thus impairing its function, or when some ureteral obstruction exists."

Hagner,¹⁴ in 1912, first observed regurgitation of fluid from the bladder to the kidney during ureteral catheterization.

Kretschmer,¹⁵ in 1915, observed clinically regurgitation of the contents of the bladder into the ureter in cystography. Direct extension of infection from the bladder through the wall of the ureter has been shown experimentally by Bauereisen.

LYMPHOGENIC INFECTIONS

Mascagni,¹⁶ in 1787, first described a lymphatic connection between the ureter and the kidney. Teichman,¹⁷ in 1861, Sappey,¹⁸ in 1874,

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Krause,¹⁹ in 1876, and Gerata,²⁰ in 1897, showed by their method of injection that there was a direct communication between the lymphatics of the bladder and those of the lower third of the ureter. Stahr,²¹ in 1900, Sakata,²² in 1903, and Bauereisen,²³ in 1910, were able to demonstrate the lymphatics in the mucous and submucous coats of the ureter, and also a network of perivascular lymphatics in the muscular and fibrous coats. The serial sections, including a section of the bladder and the intramural portion of the ureter, showed a free communication between the lymphatics of the muscular coat of the bladder and that of the ureter. The lymph current of both the bladder and the ureter is from the mucous toward the fibrous coat. The perivascular lymphatics communicate with each other in a transverse as well as in a longitudinal direction, by means of vertical and oblique branches.

Kumita²⁴ demonstrated in 1909 that the lymphatics of the kidney accompany the blood vessels. They form a capillary network in the cortex surrounding all tubules like the blood capillaries. The lymphatics of the cortex communicate with those of the capsule. This work has been confirmed by Müller;²⁵ Eisendrath and Schulz,²⁶ in 1916, Stewart,²⁷ in 1910, Sugimura,²⁸ in 1911, Hess,²⁹ in 1913, Sweet and Stewart,³⁰ in 1914, and Eisendrath and Kahn,³¹ in 1915, experimentally produced ascending infection to the kidney through the lymphatics.

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Helmholz,³² in 1922, and David,³³ in 1916, experimentally produced ascending *Bacillus coli* infection of the lumen of the ureter.

Hartzler,³⁴ in 1925, concluded that ascending infection of the kidney has not been proved.

Sugimura,²⁹ in 1911, found involvement of the lower end of the ureter in twenty-five cases of cystitis, and demonstrated that the infection extended along the lymphatics.

Carson,³⁵ in 1925 and 1927, demonstrated cancer cells in the perivascular lymphatics of the ureter, secondary to primary carcinoma of the bladder, prostate and cervix uteri, and in the perivascular lymphatics of the renal pelvis from primary carcinoma of the prostate.

TABLE 1.—Results Obtained in Series 1

Rabbit	Date of Operation, 1930	Date Killed, 1930	Organism Used*	Histologic Observations						Cultures at Necropsy
				Bladder: Cystitis	Left Ureter	Left Kidney	Right Ureter, 1 cm. Up	Right Ureter, 6 cm. Up	Right Kidney	
1	2/10	2/12	<i>S. aureus</i>	Negative	Negative	Negative	Negative	Positive†	Positive	<i>B. coli</i> from heart's blood
2	2/12	2/25	<i>S. aureus</i>	Negative	Negative	Negative	Negative	Positive†	Positive	<i>Staphylococcus</i> from bladder; <i>B. coli</i> from heart's blood
3	3/ 5	3/18	<i>S. aureus</i>	Negative	Negative	Negative	Negative	Positive†	Positive	Cultures negative
4	3/12	3/14	<i>S. aureus</i>	Positive	Negative	Negative	Negative	Positive†	Positive	<i>Staphylococcus</i> from bladder
5	3/18	4/12	<i>S. aureus</i>	Positive	Negative	Negative	Negative	Positive†	Positive	<i>Staphylococcus</i> from bladder and right kidney
6	3/19	Died 3/22	<i>B. coli</i>	Positive	Negative	Negative	Negative	Positive	Positive	<i>B. coli</i> from heart's blood and bladder

* Two-tenths cubic centimeter of an eighteen hour broth culture.

† Organisms found in perivascular lymphatics.

EXPERIMENTS

Young adult rabbits were used, with ether anesthesia and aseptic technic. Stock cultures of *Staphylococcus aureus* and *B. coli* were obtained from a human kidney by ureteral catheterization at Columbia Hospital, and the paratyphoid bacilli from Dr. Reith. A fresh eighteen hour broth culture was used in each experiment.

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TABLE 2.—*Results Obtained in Series 2*

Rabbit	Date of Operation,		Organism Used*	Histologic Observations					Cultures at Neeropsy
	1930	Date Killed, 1930		Bladder: Cystitis	Left Ureter	Left Kidney	Right Ureter, 2, 4 and 8 cm. Up	Right Kidney	
7	3/25	3/31	B. coli	Positive	Dilated	Hydro-nephrosis	Positive	Positive	B. coli from bladder
8	3/26	4/19	Para. B.†	Positive	Dilated, marked	Hydro-nephrosis	Positive	Positive	Paratyphoid bacillus from bladder
9	3/28	4/ 5	Para. B.	Positive	Dilated	Hydro-nephrosis	Positive	Positive	Paratyphoid bacillus from bladder
10	4/ 2	4/18	Para. B.	Negative	Dilated, marked	Hydro-nephrosis	Negative	Negative	B. subtilis from bladder
11	4/ 4	4/18	Para. B.	Negative	Dilated	Hydro-nephrosis	Positive	Positive	Negative
12	4/ 8	4/24	Para. B.	Negative	Dilated	Hydro-nephrosis	Positive	Positive	Paratyphoid bacillus from bladder

* Two-tenths cubic centimeter of an eighteen hour broth culture.

† Paratyphoid bacillus.

TABLE 3.—*Results Obtained in Series 3**

Rabbit	Date of Operation,		Bladder	Histologic Observations				Cultures at Neeropsy
	1930	Date Killed, 1930		Left Ureter, 2, 4 and 8 cm. Up	Left Kidney	Right Ureter, 2, 4 and 8 cm. Up	Right Kidney	
13	4/ 9	4/24	Marked cystitis	Positive†	Positive†	Positive	Positive	Negative
14	4/ 9	4/30	Moderate cystitis	Positive	Positive	Negative	Negative	Negative
15	4/15	4/30	Marked cystitis	Positive†	Positive†	Positive	Positive	Negative
16	4/22	5/ 5	Marked cystitis	Negative	Negative	Positive	Positive	Negative
17	4/23	5/ 2	Marked cystitis	Negative	Negative	Negative	Negative	Negative
18	4/28	5/14	Trigonitis	Negative	Negative	Negative	Negative	Negative

* One cubic centimeter of an eighteen hour broth culture of paratyphoid bacillus was injected into the bladder.

† Organisms found in the perivascular lymphatics.

Series 1.—A midline incision, 4 cm. in length, was made below the umbilicus, the coils of the intestines were packed off with a warm gauze pack, and the right ureter was located as it crossed the iliac artery; at this point the posterior layer of peritoneum was opened and the ureter delivered. A very fine needle was used for injection into the ureteral wall 2 cm. proximal to the bladder, after which mercurochrome-220 soluble was applied to the site of the puncture, the ureter

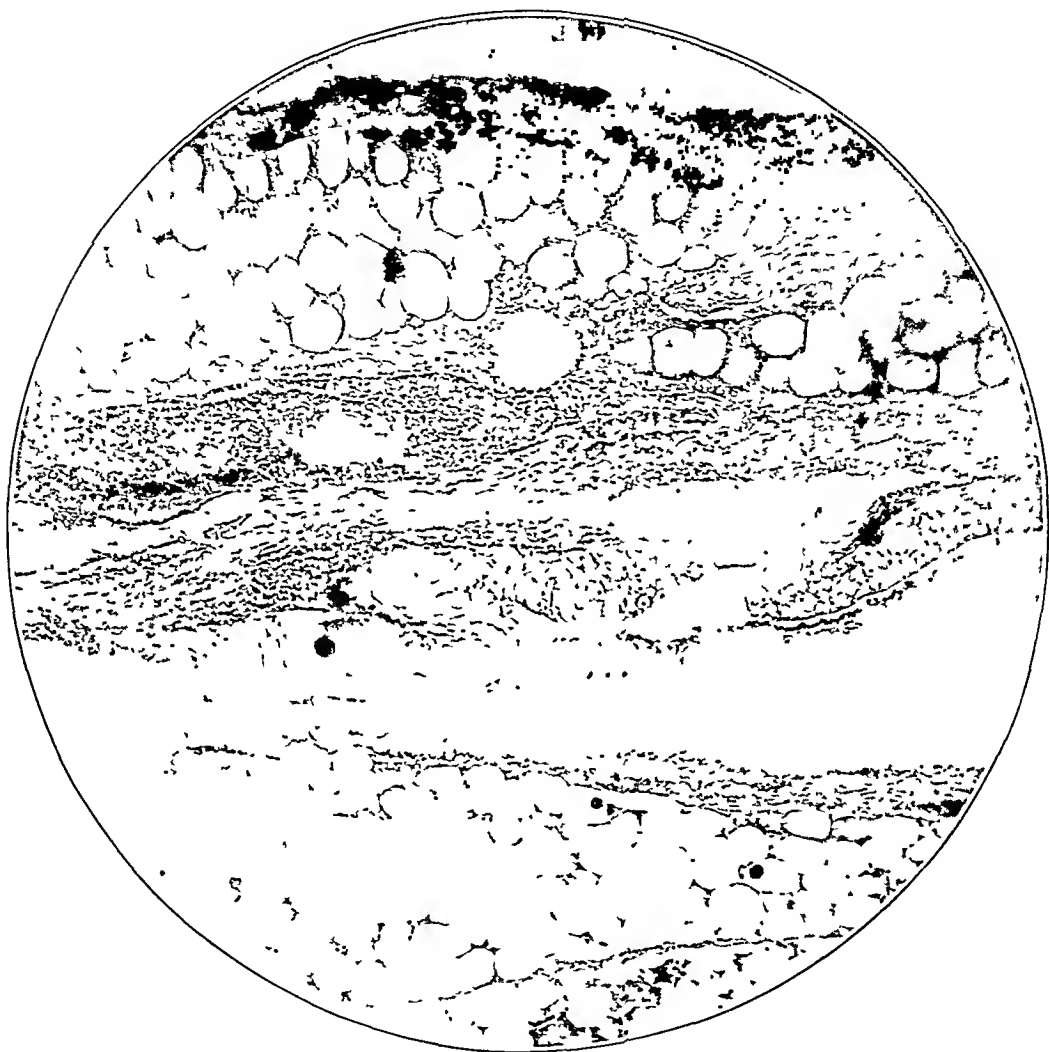


Fig. 1 (rabbit 4).—Photomicrograph of the right ureter, 1 cm. down, showing proliferation of lymphatic endothelium and an infiltration of lymphocytes.

dropped back, the pack removed and the abdomen closed in layers, silk, cotton and collodion dressings being applied.

Series 2.—Through a midline incision the left ureter was freed from its peritoneal attachment, from the iliac artery to the bladder, a silk ligature was applied to the ureter at the wall of the bladder, and at a point 1.5 cm. proximal to the bladder, the ureter between these ligatures was then excised for microscopic examination. The right ureter was then located, and the injection was made into

the ureteral wall at its junction with the wall of the bladder. Mercurochrome-220 soluble was applied to the site of the puncture, and the abdomen was closed.

Series 3.—A midline incision, 3 cm. in length, was made over the bladder through the skin and linea alba, and the bladder was delivered without opening the peritoneum. Sufficient pressure was applied to the wall of the bladder to force the urine through the urethra, after which 1 cc. of an eighteen hour broth culture was injected into the fundus of the bladder with a fine needle. Mercuro-

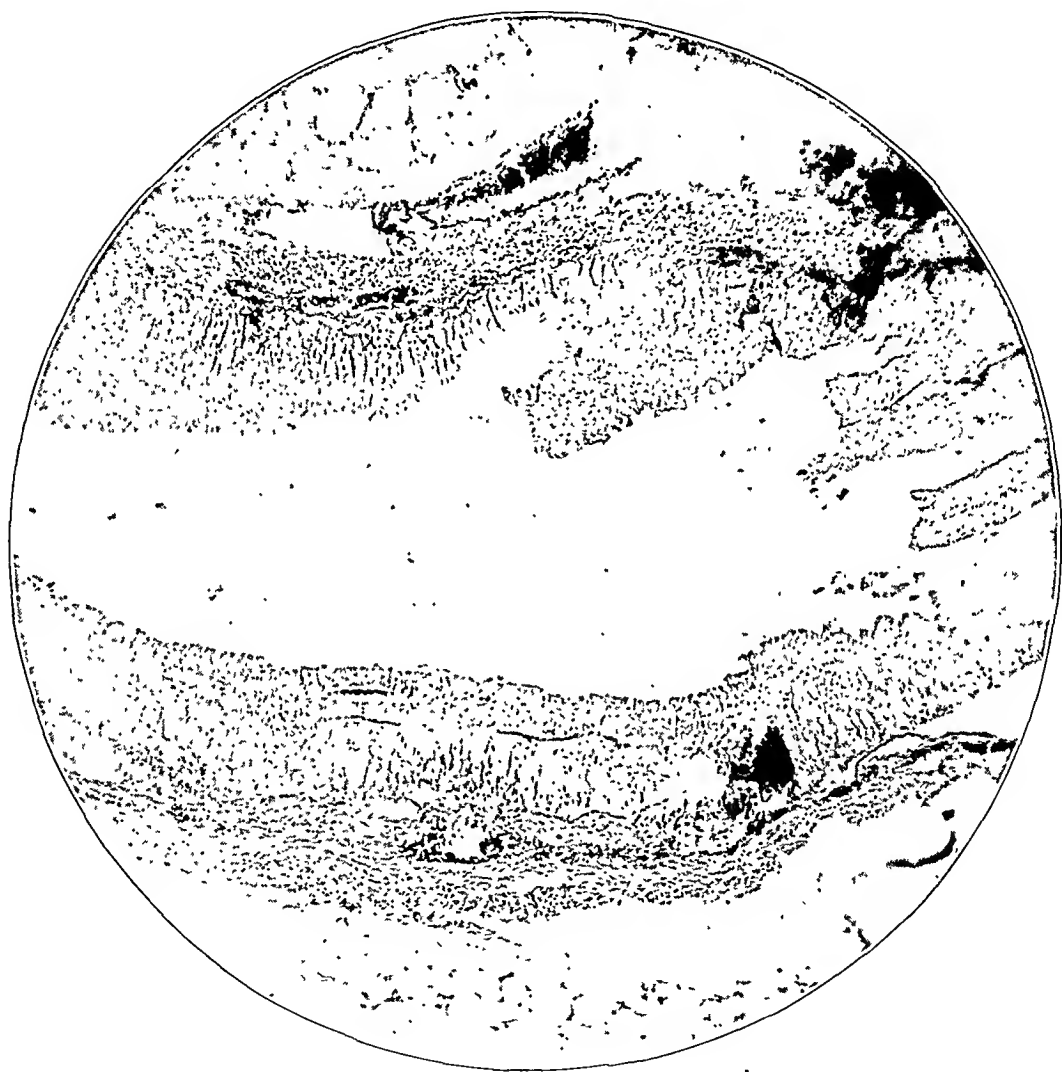


Fig. 2 (rabbit 6).—Photomicrograph of right ureter, 1 cm. down, showing perivascular infiltration of lymphoid cells.

chrome-220 soluble was applied to the site of the puncture, after which the bladder was replaced in the pelvis and the wound closed as in the previous series.

The animals were killed from two to forty-six days after the operation, and an autopsy was performed. Cultures were made from the heart's blood, the peritoneum, each kidney and the bladder.

The tissues were fixed in 10 per cent formaldehyde and embedded in paraffin. Longitudinal sections were cut from each ureter, 1, 2, 4 and 8 cm. above the

bladder, and sections were cut from the bladder and from each kidney to include the pelvis. All were stained with MacCallum tissue stain.

Histologic Observations.—In series 1, the right ureter showed the mucosa to be intact above the point of injection, with the epithelial cells distinct in outline, with well stained nuclei. In the submucosa there was an infiltration of lymphocytes, a proliferation of lymphatic endothelium and, in areas, a perivascular lymphoid infiltration. This infiltration extended into the muscular layer and, in

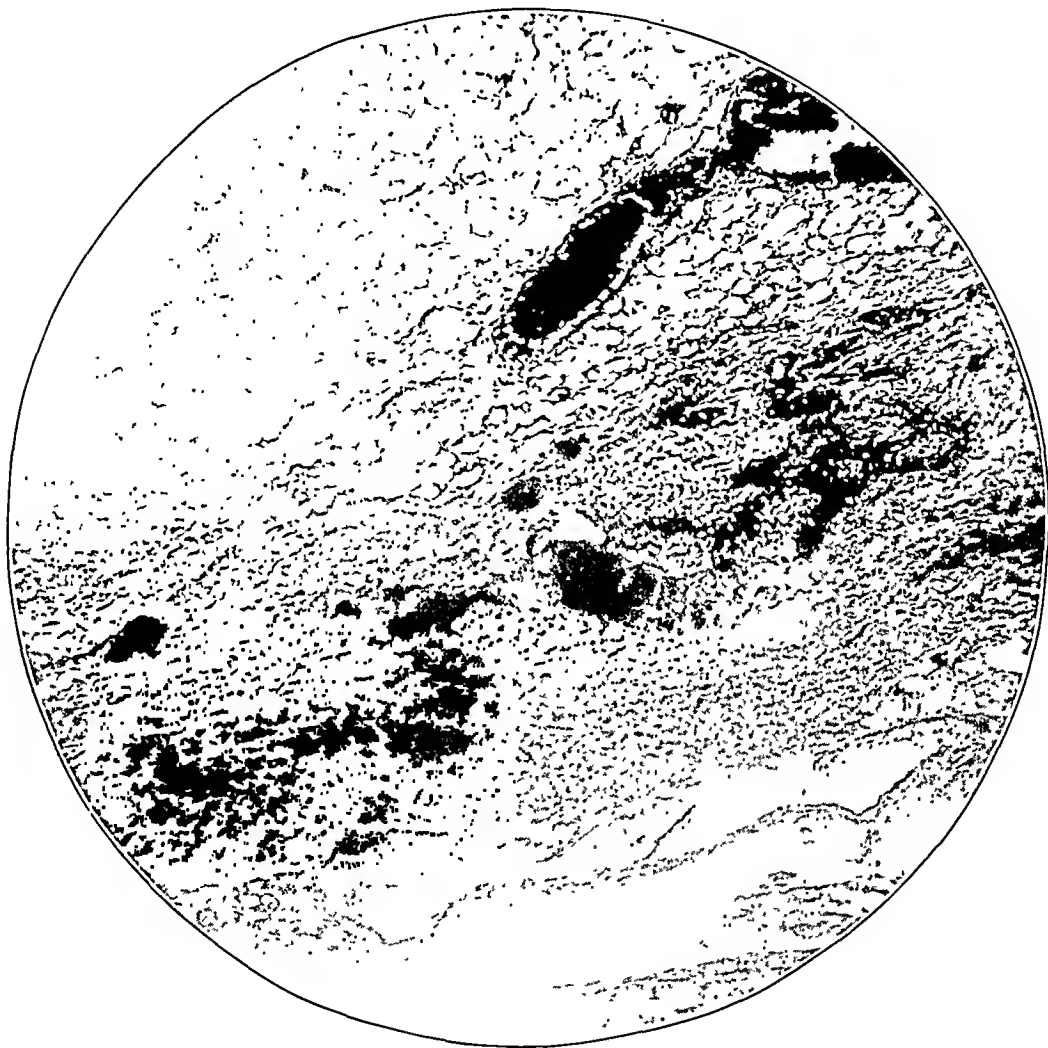


Fig. 3 (rabbit 12).—Photomicrograph of right ureter, 1 cm. down, showing marked proliferation of lymphatic endothelium and an infiltration of lymphocytes.

a few areas, into the adventitia. The inflammatory infiltration followed the lymphatics of the submucosa into the renal pelves, and the kidneys showed a perivascular infiltration of lymphocytes. In the first five experiments, staphylococci were observed in the submucosa. All sections from the left kidney, ureter, bladder and right ureterovesical orifice were normal.

In series 2, the right ureters and kidneys showed essentially the same histologic picture as those in series 1, except that the organisms injected could not

be seen. Sections from the left ureters, removed at operation, were all normal, sections above the ligatures showed a thinning out of the muscular layer, and in rabbits 8 and 10 sections from the left ureters, 4 cm. up, showed a marked proliferation of young connective tissue cells with newly formed blood vessels.

The left kidneys showed a marked dilatation of the tubules with a flattening out of the renal epithelium in areas. Sections from the bladders showed the mucosa to be poorly stained and, in areas, covered with lymphoid cells. In the

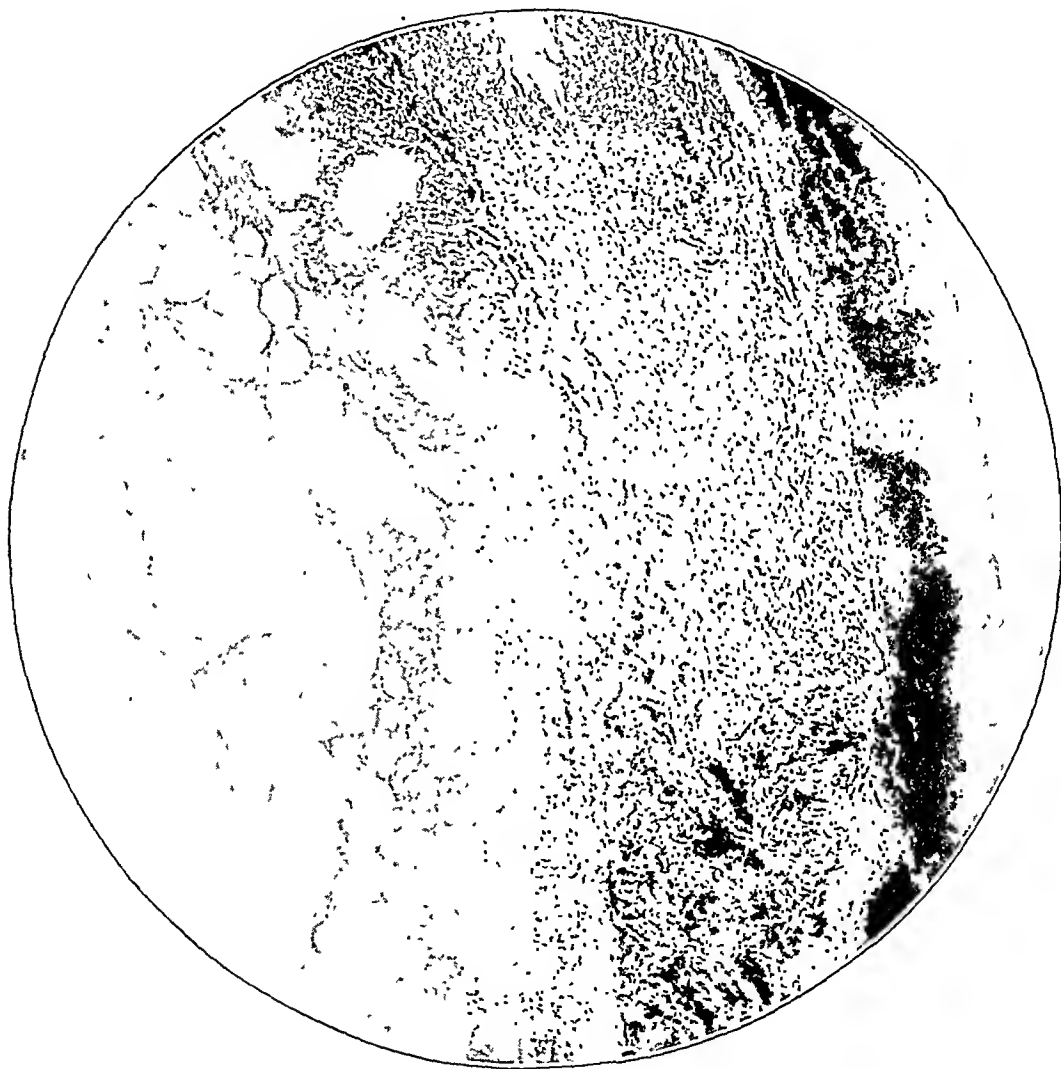


Fig. 4 (rabbit 15).—Photomicrograph of right ureter, 1 cm. up, showing infiltration of lymphoid cells in the submucosa and muscular layers, with a few polymorphonuclear leukocytes.

submucosa marked infiltration of lymphoid cells was seen, with perivascular infiltration in the muscular layer.

In series 3, sections from the bladders showed the mucosa to be absent in areas. In other areas, the epithelial cells were swollen and indistinct in outline, with poorly stained nuclei; large numbers of epithelial cells were fragmented; in areas the mucosa was covered with lymphocytes, polymorphonuclear leukocytes

and fibrin. The submucosa showed a marked infiltration of lymphoid cells, with an occasional polymorphonuclear leukocyte. In the muscular layer a marked perivascular infiltration of lymphocytes was seen. Sections from the right and left ureters in rabbits 13, 14 and 15 and from the right ureter in rabbit 16 showed the mucosa to be well preserved, with a perivascular infiltration of lymphoid cells, which in areas extended into the muscular layer; in rabbits 13 and 15 the organisms were observed in the submucosa.

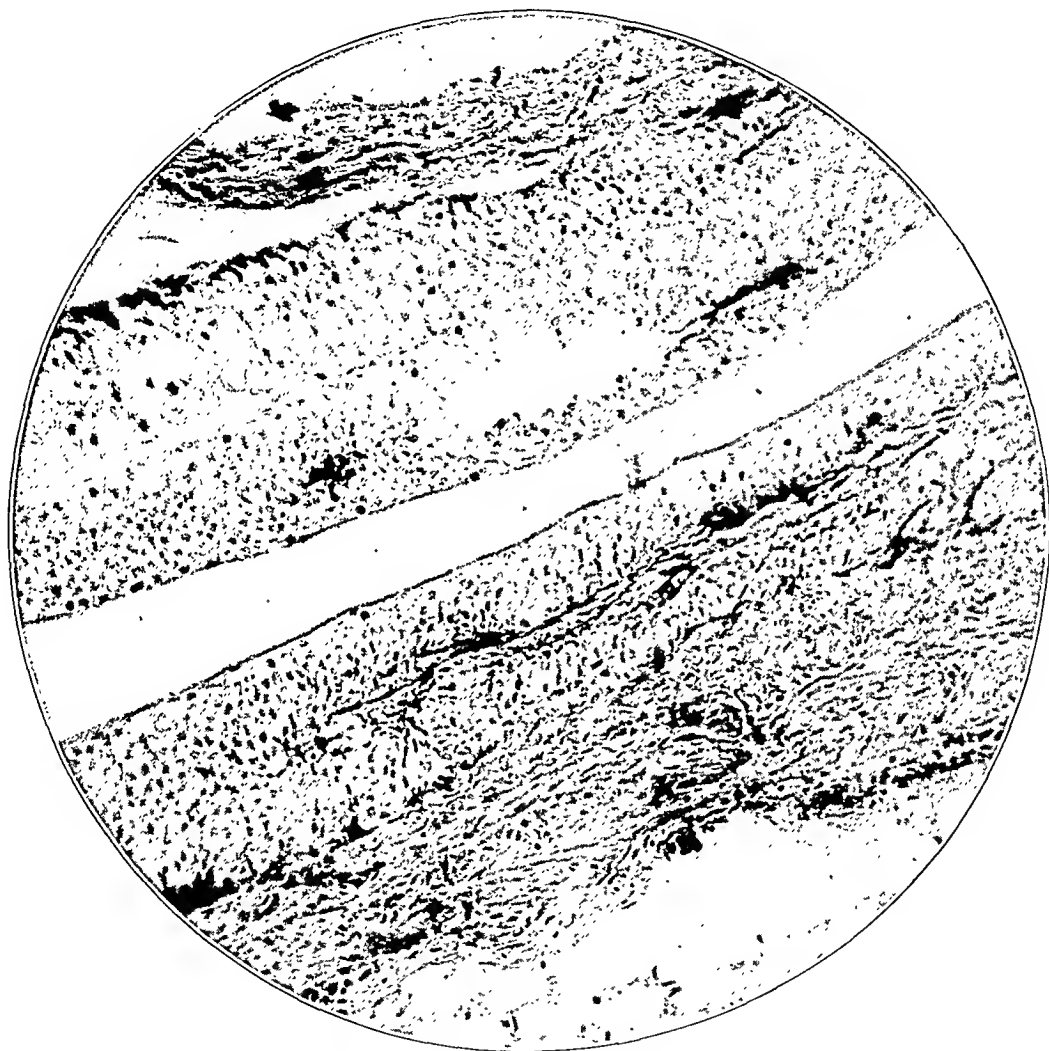


Fig. 5 (rabbit 15).—Photomicrograph of left ureter, 5 cm. up, showing mucosa well preserved with a perivascular infiltration of lymphoid cells, which infiltrates into the muscular layer.

Sections from the ureters in rabbits 16 (left), 17 and 18 (right and left) showed no changes. Sections from the right and left kidneys in rabbits 13, 14 and 15 and from the right kidney in rabbit 16 showed a perivascular infiltration of lymphoid cells, which extended into the interstitial tissue in areas; sections from the left kidney in rabbit 17 and from the right kidney in rabbit 18 showed no noteworthy changes.

CONCLUSIONS

Infection produced experimentally in the lower end of the ureter or wall of the bladder has been demonstrated to pass upward through the perivascular lymphatics to the kidneys.

The author was assisted by Dr. T. L. Squier, Director of the Department of Preventive Medicine, and Dr. Allen Reith, Bacteriologist, A. O. Smith Corporation. Mr. Leo Massapust, artist, Marquette University, furnished the photomicrographs.

425 East Wisconsin Avenue.

CARCINOMA OF THE BREAST IN THE YOUNG*

BURTON J. LEE, M.D.

NEW YORK

Cancer of the breast in subjects 40 years of age or under is not a rare occurrence. A recent survey of the admissions to the Memorial Hospital from Jan. 1, 1917 to Jan. 1, 1929 showed that 2,663 patients with cancer of the breast had sought admission during this period.¹ The research further revealed that 17.33 per cent (or approximately one sixth) of all patients with cancer of the breast were 39 years or younger. The incidence of mammary cancer in persons in the younger age periods must be borne in mind, otherwise errors in diagnosis will inevitably occur and unfortunate end-results follow.

The material for this paper was furnished by a study of 303 patients admitted to the breast clinic of the Memorial Hospital prior to November, 1926. Radical mastectomy was performed on 191 patients, presenting presumably operable cases at the time of operation. In 44 a radical operation was performed at the Memorial Hospital; in 32 operation was done in other hospitals in New York and the patients were then referred to the breast clinic for postoperative irradiation; 115 patients came to the clinic with recurrent phases of the disease, radical amputation having been done elsewhere. In addition, 52 patients in this series were admitted to the clinic following local mastectomy, local excision or a delayed radical operation after local excision; in many of these patients also the disease was recurrent at the time of admission. The study also includes a survey of 60 patients in the primary inoperable group who had not received surgical treatment, but who were treated by irradiation.

My associates and I have been more impressed year by year with the poor end-results following radical surgical intervention in cases of cancer of the breast in young women; few patients are encountered who survive the three year period. Following operation, the disease is often more rapid in its course, even though examination before operation reveals a well localized process in the breast without apparent involvement of the axillary nodes, recurrences appear earlier and there is usually a fatal termination. This survey was undertaken to determine the exact end-results in this group, and to discover if possible some of the factors contributing to these results.

* Submitted for publication, Nov. 12, 1930.

* From the Breast Clinic of the Memorial Hospital.

1. Pack, George T., and LeFevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York, *J. Cancer Research* **14**:167, 1930.

FACTORS CONTRIBUTING TO THE END-RESULTS OF OPERATION

Age.—Two women, aged 22, were the youngest patients in the entire group. The distribution of patients in five year periods according to age at the time of the inception of the disease is given in table 1.

Mammary cancer is rare in patients 25 years or under, but 3 per cent of our patients under 40 fell within this age period. The occurrence of mammary cancer increases in the older patients, approximately one third of the group being between the ages of 31 and 35, and one half in the five year period from 36 to 40.

TABLE 1.—*Distribution of Patients with Cancer of the Breast According to Age*

Five Year Age Period	Number of Patients	Percentage
21 to 25.....	9	3
26 to 30.....	42	14
31 to 35.....	94	31
36 to 40.....	155	52
Total.....	303	100

TABLE 2.—*Previous Lactation*

	Patients	Percentage
Yes.....	179	66
No.....	91	34
Total.....	270	100

TABLE 3.—*Preoperative Diagnostic Errors*

Diagnosis of carcinoma not positively made.....	18
Fibro-adenoma.....	9
Benign.....	5
Abscess.....	2
Mastitis.....	1
Cyst.....	1
Papillary cyst adenoma.....	1
Total.....	37

Previous Lactation.—In 270 patients, data were available to determine whether previous lactation had occurred in carcinomatous breasts; the results are given in table 2.

An inspection of this table shows that exactly two thirds of the patients had previously had lactating breasts, whereas one third of the patients had never lactated.

Diagnosis.—The diagnosis of cancer of the breast in the young woman is often attended with difficulty. In the cases reported here a preoperative diagnosis of a benign lesion was made thirty-seven times. Table 3 indicates diagnostic errors prior to operation.

If, for the moment, the 60 primary inoperable cases are subtracted from the total number of 303, leaving 243 in which a preoperative

diagnosis was recorded, it will be seen that a correct diagnosis of mammary cancer was not made in 15 per cent of the cases, a definitely higher figure than one obtains when women in the older age groups are studied. In 18 patients the surgeon suspected that he was dealing with mammary cancer, but could not reach a positive diagnosis of malignancy.

In nine patients the preoperative diagnosis was fibro-adenoma, the error in three cases having been made by me. One cannot stress too much the difficulty in differentiating between a fibro-adenoma and true infiltrating carcinoma in the breast of a young woman. Not infrequently, one may encounter a small infiltrating cancer, which on physical examination gives all of the classic symptoms of a fibro-adenoma. There may be no alteration in the position of the nipple, no adherence of skin over the tumor, and the mass itself may appear sharply circumscribed with a definite sense of mobility in the surrounding tissue of the breast. In the light of these experiences, one should always keep in mind that a tumor in a young woman's breast, which is apparently nothing but a simple fibro-adenoma, may really be true infiltrating carcinoma, and therapeutic measures should be outlined with this possibility in view.

In five cases the diagnosis of benign tumor was made, but the exact character of the lesion was not indicated in the records available.

In two patients a diagnosis of abscess of the breast was made, when the patient was really suffering from a rapidly growing inflammatory carcinoma.² I have discussed this difficulty in diagnosis in a previous paper. When the surgeon commits this error, and the breast is incised in an attempt to evacuate an abscess, the patient is subjected to serious additional hazard, with the possibility of further dissemination of the disease.

In one patient a diagnosis of papillary cyst adenoma was made, and operation revealed a papillary cyst adenocarcinoma. The differential diagnosis between these two conditions is always difficult whatever the age of the patient, for in both instances one finds a sharply encapsulated tumor with a history of bloody discharge from the nipple, and I know of no method of physical examination which will make this differentiation.

Six patients, comprising 2 per cent of the entire group, were colored. I have noted the comparatively small number of young colored women coming to the clinic suffering from mammary cancer. One may doubt whether this small percentage of colored patients in the series is of significance. Only a complete survey of a large group of colored patients can demonstrate how frequently mammary cancer occurs in young colored women. Such a study can only be made in a hospital to which a large number of colored patients are admitted.

2. Lee, B. J., and Tannenbaum, N. E.: *Inflammatory Carcinoma of the Breast*, *Surg. Gynec. Obst.* **39**:580 (Nov.) 1924.

Only 1 patient of the entire 303 was a man, comprising 0.3 per cent of the total group. It would seem apparent that cancer of the breast is rare in men, 40 years of age or under, a point which should be kept in mind in reaching a diagnosis in tumors of the male breast.

INFLAMMATORY CARCINOMA OF THE BREAST

In a previous communication, 28 cases of inflammatory carcinoma of the breast were studied. In that series 10, or 36 per cent, occurred in young women, so that our experience thus far at the clinic has shown that approximately one third of the inflammatory carcinomas occur in women, aged 40 years or under. Of the 303 cases in the present series, 26, or 9 per cent of the entire group, were classified as typical examples of inflammatory carcinoma. This is unquestionably the most menacing and rapidly progressive form of mammary cancer. At times the disease resembles an acute infectious process. Physical examination shows

TABLE 4.—*Duration of Life in Young Women with Inflammatory Carcinoma*

Inoperable Cases (When First Seen the Disease Was Widespread and Far Advanced):		
Shortest duration		4 months
Longest duration	2 years, 3 months	
Average duration	1 year	
Patients Subjected to Radical Operation:		
Shortest duration		11 months
Longest duration	2 years, 3 months	
Average duration	1 year, 11 months	
End-Results:		
Dead		26 patients

the affected breast to be definitely larger than normal, with a distinct pinkish blush over it, which may extend well beyond the confines of the breast. The tumor is poorly defined, though usually palpable. The nipple is frequently edematous and retracted, and axillary nodes on the same side are involved early and are usually bulky. Palpation may elicit slight tenderness over the breast, and the temperature taken beneath it may show a rise of from 1 to 1.5 degrees F., as compared to that taken in the mouth. The opposite breast and nodes are also invaded early. We have not seen a case of inflammatory carcinoma of the breast in a young woman which has yielded any but disastrous results following an attempt at radical operation. Recurrence following operation occurs quickly, often immediately, and the whole process frequently spreads over the entire wall of the chest and at times down over the abdomen, around the lateral wall of the chest and onto the back. The only therapy available at the present time which is capable of restraining the growth of these inflammatory carcinomas in young women is adequate irradiation. Table 4 indicates the duration of life in the patients with inflammatory carcinoma.

The histories of several cases are appended which will illustrate the frightfully rapid course of this form of the disease.

REPORT OF CASES

CASE 1 (no. 174).—N. B., aged 37, married, white, a native of Ireland, had borne four children, two of whom were alive and well. All of the children nursed for a period of approximately one year. Five months before admission to the clinic, the patient fell, striking her right breast against some stiff shrubbery. Following the fall, she suffered from chills and fever and noticed that her right breast was hard, red and swollen. The physician who saw her at that time assured her that she need have no worry concerning the condition of the breast. It, however, remained hard and continued to increase in size. Two months before admission she first noticed a swelling of the right arm which extended down to the hand, and at the same time she became aware of several lumps in the right axilla and right supraclavicular region. For the two months before admission she was unable to abduct the right arm.

Physical examination showed a woman in good general condition. The right breast was enlarged, heavy and thickened throughout, and the skin over it showed a "pigskin" appearance. The nipple was flattened. The skin overlying the breast was irregular and mottled with red patches, some of which were indurated. There was a large mass of nodes in the right axilla, fulness in the right infraclavicular region and enlarged nodes in the right supraclavicular fossa. Examination of the chest at this time showed a few, fine, inconstant, crackling râles over the upper right interscapular region and at the base of the right lung posteriorly, where a slight diminution of breath sounds was noted. There were signs suggestive of metastasis. A roentgenogram of the chest made at the time of admission did not reveal definite evidence of metastasis. A thermometer placed in the right axilla registered 100, and in the left axilla, 98 F.

At the time of admission the patient was suffering considerable pain in the right hand and arm. She was given a cycle of high voltage roentgen treatments, consisting of four treatments over the right breast and drainage areas, the set-up being, time, eighty minutes; milliamperes, 4; spark gap, 90; filters, 0.5 mm. of copper and 1 mm. of aluminum, and focal distance, 50 cm. The patient left the hospital against advice and never returned. A biopsy taken while she was in the hospital showed a cellular, infiltrating carcinoma with considerable fibrosis. The cells were large, probably of the sweat gland type. The follow-up on the patient revealed that she died two months after discharge from the hospital, seven months after the beginning of the symptoms.

CASE 2 (no. 222).—G. M., a colored woman, aged 38, married, was born in the United States. She had borne three children, each of whom she had nursed about seven months. She had never suffered a trauma to the breast. Six months before admission to the clinic she noticed a small lump in the right breast which increased steadily in size until it involved the entire breast. It was unattended by pain until two months before admission, when she began to have pain in and about the right shoulder which increased in severity up to the time of admission. She had complained of a slight cough during the month before her entry into the hospital.

Physical examination showed a woman in fair general condition with apparent emaciation. The right breast was entirely filled with a hard solid tumor. The skin over the breast was thickened and corrugated. The nipple was flattened, and the whole breast was shrunken and fixed to the wall of the chest. A large chain

of nodes extended up to the axilla and through the outer part of the infraclavicular region to the supraclavicular space and neck. There was definite local heat over the breast on palpation, with a reddening of the skin which showed a sharp line of demarcation. Examination of the chest at this time showed dullness at the base of the left lung and a few fine crackling râles at the base of both lungs. A roentgenogram of the chest made at the time of admission showed a thickened pleura and fluid in the left side of the chest, displacing the heart shadow to the right, with further evidence of metastasis in the right side of the chest also.

Treatment by irradiation was begun shortly after admission, three high voltage roentgen treatments being given to the right side of the chest with a set-up of: time, eighty minutes; milliamperes, 4; 0.5 mm. of copper and 1 mm. of aluminum; spark gap, 90 cm. at a focal distance of 50 cm. A month after treatment the

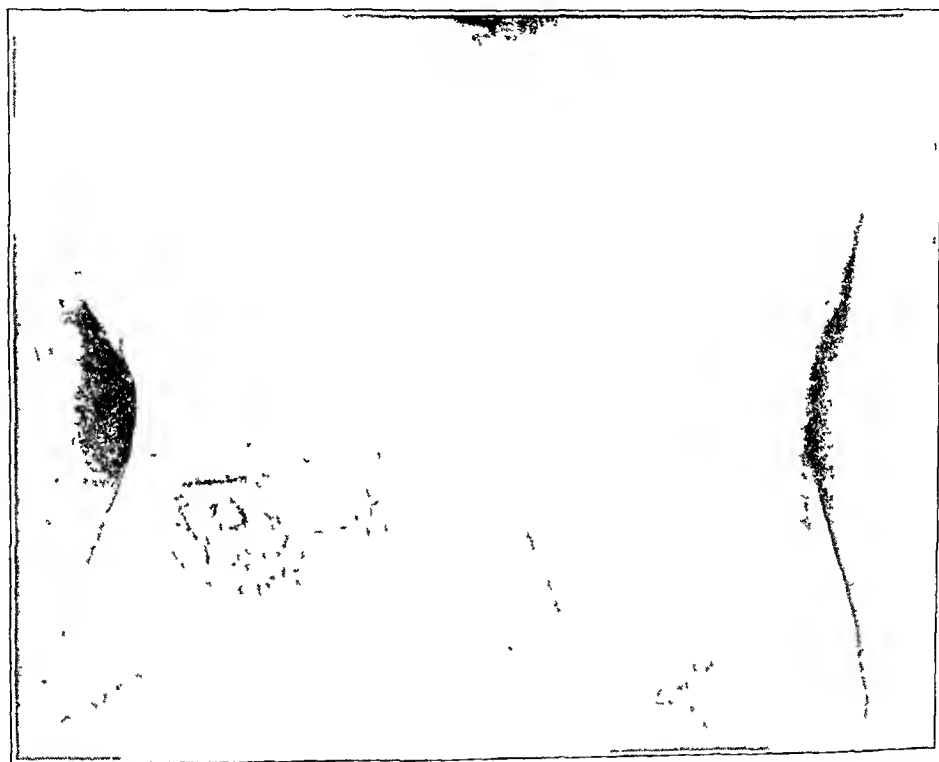


Fig. 1 (case 222).—Primary inoperable carcinoma of the breast, inflammatory type.

patient was somewhat improved with slight regression in the size of the tumor and less pain, but she did not return to the clinic from that time until her death which occurred ten months after admission, and one year and four months from the beginning of symptoms.

CASE 3 (no. 179).—E. C., aged 30, a married white woman, had borne two children, the youngest 19 months old. She had nursed this child for fourteen months, and when the child was weaned (five months before the admission of the patient to our service) she first noticed that the right breast did not return to normal. Her physician advised the use of a breast pump, but there was no change in the size of the breast following this procedure. She consulted a surgeon two months later, who made a diagnosis of abscess of the breast, and a surgical operation was performed with the idea of evacuating an abscess. A few weeks later a

biopsy was made on the small, reddened cutaneous nodule above the breast, and this histologically also proved to be malignant. Six weeks before admission the left breast became infiltrated with tumor tissue. Prior to admission she had received several roentgen treatments to both breasts, with some regression in the size of the tumors.

On admission five months after the beginning of symptoms, there was a diffuse infiltration of both breasts involving all of the organs, with marked reddening over the whole anterior wall of the chest. Nodes were present in both axillae and in the supraclavicular fossae. Examination of the chest strongly suggested metastasis. A poor prognosis was given and a fatal termination predicted within a few months. Roentgen treatment was suggested as the only possible palliation for the disease. The patient returned to her surgeon and received several roentgen

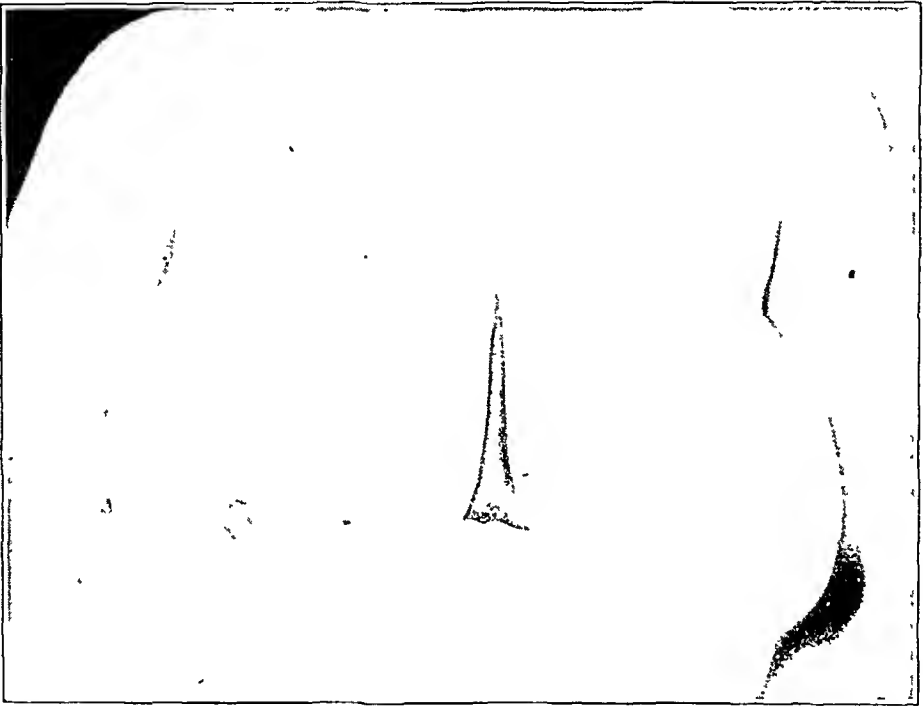


Fig. 2 (case 255).—Primary inoperable carcinoma of the breast, inflammatory type. Note the slightly darker hue of the right breast and adjacent arm.

treatments, but the disease rapidly progressed, and she died four months after admission to our service. The total duration of the disease was nine months.

CASE 4 (no. 255).—B. W., aged 33, a married woman, was born in Russia of Hebrew parents. She had borne four children and had nursed each child for one year, using both breasts equally. The last child was born two years before her admission to the Memorial Hospital. No unusual condition had occurred in the breast in connection with lactation. She stated that the right nipple had always been more prominent than the left and that the right breast had always been larger. Two months before admission she first noticed a hardening of the right breast and a retraction of the right nipple. There had been no pain or discharge from the nipples. She thought that she had lost weight recently.

Physical examination showed a woman in good general condition. The right breast was larger than the left, the right nipple was elevated and retracted, with

some fixation of the nipple to the underlying structures. The skin had a definite "pigskin" appearance over the lower segment of the breast. There was a distinct pinkish blush over the whole breast, which ran in oblique fashion upward and inward to the tip of the sternum, with increase of local heat on palpation over this breast. In the middle and outer segment of the breast there was a poorly defined mass 8 by 5 cm. There were several enlarged soft nodes in the right axilla but none in the supraclavicular region. Examination of the chest gave negative results, and the roentgenogram of the lungs did not show definite evidence of metastasis. A diagnosis of inflammatory carcinoma of the breast was made, and treatment by irradiation was begun.

The treatment consisted of three high voltage cycles of four treatments each to the right breast and drainage areas over a period of seven months, the set-up being: time, ten minutes, using the water cooled tube, milliamperes, 30; 6.5 mm. of copper and 1 mm. of aluminum; spark gap, 90 cm., at a focal distance of 50 cm. In addition, the breast itself was also treated with the radium element pack, using 20,000 millicurie hours with exposed area of 70 sq. cm., a filtration of 2 mm. of brass at a distance of 6 cm., the dose being divided through two portals. Following these treatments there was a slight but not marked regression in the tumor. Four months after admission the patient began to complain of pain over the lower portion of the thoracic spine. Although a roentgenogram of the spine was negative, one high voltage roentgen treatment was applied over this area with the set-up described before. Five months after admission the patient had a miscarriage at one month, and a short time later a curettage was performed at another hospital. The following month, on return to the clinic, there had been considerable regression in the size of the tumor in the breast. At the same time a roentgenogram of the chest showed no evidence of metastasis. Four months later, which was one year after the beginning of symptoms, roentgenograms of the pelvis showed extensive metastasis of the osteoplastic type. An irritable cough had developed, and a thickening at the base of the left breast was reported. The disease from this time on progressed steadily, and the patient died one year and two months from the time of admission to the service and one year and four months after the beginning of symptoms.

PRIMARY INOPERABLE CARCINOMA

Including those with inflammatory carcinoma, sixty patients at the time of their admission to the hospital had advanced primary inoperable cases, in which no thought of radical operation could be entertained. Many of these patients had reached the stage of inoperability a few months from the inception of symptoms, illustrating how rapid had been the course of the disease. They were treated by external irradiation, the high voltage apparatus being generally used. The majority so treated showed some regression in the local disease, but there seemed little doubt that the course of the disease was materially altered by the irradiation. Today we feel certain that mammary cancer must be given adequate irradiation if a considerable degree of restraint in growth is to be obtained by this means, and I know that the irradiation given these patients was inadequate. Others with widespread disease and in poor general condition received little or no irradiation, for treatment would have been futile.

In this group, the shortest duration of life from the beginning of symptoms to death was two and one-half months, another patient survived four months, a third four and one-half months, and but two lived six months. Five patients in whom the course of the disease was less rapid were still living with evidence of disease more than five years after the beginning of symptoms. The average duration of life for the entire sixty was one year and eleven months, while 30 per cent died within one year.

In addition to the case histories of primary inoperable carcinoma of inflammatory type recorded, a few additional histories indicate the rapid course of the disease.

REPORT OF CASES

CASE 5 (no. 121).—C. L., aged 29, a married Jewess, born in Austria, gave birth to one child four and a half years before admission, which she nursed for thirteen months equally on both breasts. She stated that when she was three months pregnant she had had what was called mastitis in one breast, she thought the left. There had been no trauma to the breast. She said that two weeks before admission she noticed a hardness and tenderness in the left breast. She had had no cough and no loss of weight.

Physical examination showed an apparently healthy white woman in good nutrition. Both breasts were large and pendulous with well formed nipples and areolae. In the left breast there was an irregular, hard, nodular mass, posterior and above the areola, measuring 6 cm. in diameter. Definite retraction of the skin could be made out over the tumor. There was a slight tendency to "pigskin" appearance over the left breast. Sizable firm nodes were palpable in both axillae. General physical examination showed that the mucous membranes were pale. There was deep tenderness over the whole right side of the abdomen, but no tenderness of a specific nor abnormal mass could be palpated, and the edge of the liver could not be felt. Pain was elicited in the region of the first and second lumbar vertebrae on movement of the spine, but no tenderness could be detected here. The x-ray films of the pelvic region showed numerous and extensive areas of metastasis. The patient was admitted to the hospital, and the day after admission complained of pleuritic pain in the right side which subsided in a few days with rest in bed and strapping of the chest. A roentgenogram of the chest made at this time still showed no evidence of metastasis.

The patient was treated with radium element pack over the breast and drainage areas, using 20,000 millicurie hours over the left breast at 6 cm. with 1.5 mm. of brass and 0.35 mm. of platinum filter. Sixteen thousand millicurie hours of treatment were given in a similar manner over the left axilla, and 8,000 millicurie hours over the left supraclavicular region. In addition, 20,000 millicurie hours were given over the lumbar spine and a high voltage roentgen cycle of four treatments was applied to the pelvis using 185 kilowatts, 0.05 mm. of copper and 1 mm. of aluminum filter, target skin distance of 50 cm., over a field of 8 by 10 cm., 30 milliamperes of current with twelve minute exposures.

A blood count made as the treatment was finished showed: hemoglobin, 60 per cent, with red cells, 3,064,000; white cells, 3,400; polymorphonuclears, 57 per cent; large lymphocytes, 10; small lymphocytes, 15; transitionals, 14; eosinophils, 3, and basophil, 1. Three and one-half weeks later the hemoglobin had dropped to 35 per cent, the red cells to 1,856,000 and the white cells to 2,600 with the differential

count not significantly altered. Unfortunately a blood count was not made on admission, so that it is impossible to state how much of the anemia was due to the disease and how much to the irradiation, but it is probable that both contributed. The patient left the hospital, but never returned. The disease progressed with alarming rapidity, and she died four months after her admission, and four and a half months after the beginning of the symptoms.

As one reviews this case, it seems evident that the irradiation applied did not stay the course of the disease, and it seems not improbable that it may have hastened the death of the patient. Moreover, the degree of response of the tumor in the breast to irradiation showed that the neoplasm was a radioresistant type in which irradiation is of comparatively little value.

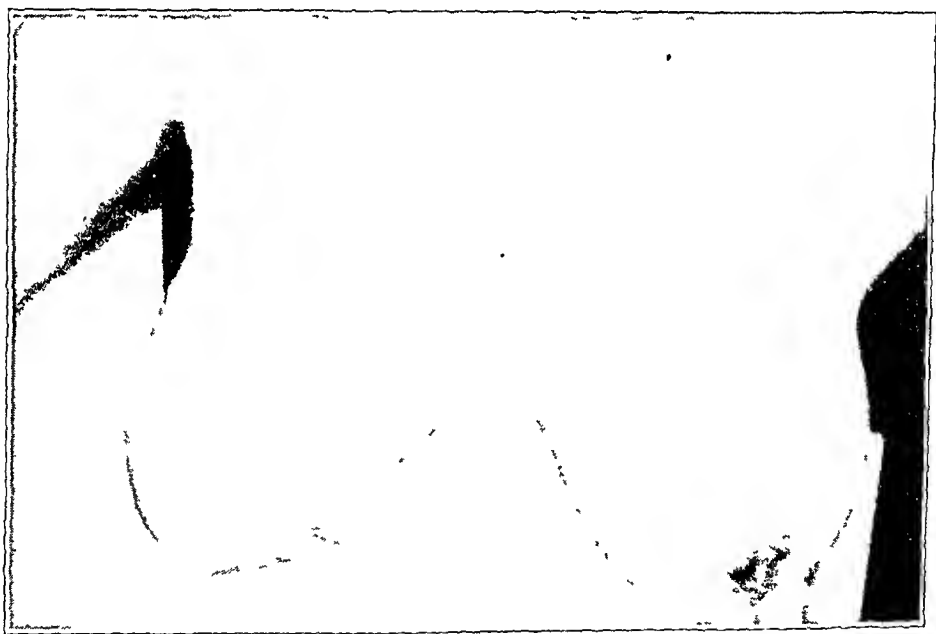


Fig. 3 (case 121).—Primary inoperable carcinoma of the breast. The left breast is slightly larger than the right. Few local symptoms were evident on inspection, although the patient at this time was suffering from widespread metastasis.

CASE 6 (no. 225).—M. N., aged 40, a white woman, born in the United States, single, had had no history of trauma to the present or any abnormal mammary history. Nine months before admission she noticed a lump the size of a marble in the center of the left breast beneath the nipple, unattended by pain or tenderness.

Physical examination showed a woman in good nutrition. The left breast was almost completely occupied by a mass 13 by 14 cm. with retraction of the nipple and fixation of the skin over the mass and an area of ulceration 2 cm. in diameter over the tumor which was fixed to underlying structures. One advertent node was palpable in the left axilla. The supraclavicular region was normal. Examination of the chest showed diminished resonance and decreased breath sounds from the third rib to the apex of the left lung, but no râles could be heard. Close to the midsternal line opposite the third rib were three shotty nodules in the skin.

The discharge from the ulcerating mass was foul and a local mastectomy was deemed advisable to free the patient from her disagreeable condition.

A local mastectomy was done in which a wide elliptical incision was made, and the whole wound was left open save for one or two traction sutures at its extremities. At operation it was found that the muscles were extensively involved, and the incision passed through carcinomatous tissue at the lower edge of the axilla. An attempt was made to close in the axilla by sutures. The histologic report of the tissue, made by Dr. Ewing, showed that the breast was large, firm and fat. The nipple and skin for a zone of 5 cm. was excoriated, scaling and indurated, and for a zone of 8 cm., the skin was indurated and thickened as by infiltrating carcinoma. The area around the nipple was enlarged, and it fused with the underlying tissues into a dense, inelastic cone-shaped mass, the base break-



Fig. 4 (case 225).—Primary inoperable cancer of the breast. The left breast was completely occupied by tumor.

ing up into a series of isolated cicatricial areas throughout the larger area of the breast. Firm areas appeared on the borders of the breast. None of the areas showed chalky points, but the diagnosis of carcinoma in the nipple and other areas was based on the induration. Three considerable layers of muscle were quite firmly attached to the under surface of the breast, but no definite invasion of the process into the muscle could be seen. The microscopic report revealed: infiltrating carcinoma, large opaque cells throughout all of the suspicious areas, infiltration of the muscles, and wide infiltration of the skin. Three weeks later the granulating surface was grafted by the Thiersch method, the grafts being removed from the left thigh. The patient left the hospital and did not return for postoperative irradiation. The disease progressed rapidly, and she died four months after the palliative mastectomy, with evidence of advanced disseminating disease.

In reviewing this case one feels certain that the effort to rid the patient of a foul ulcerating mammary cancer by palliative mastectomy was unwise and that some form of palliative irradiation might have carried her along equally as well or better than did the attempt at operation. If palliative mastectomy is to be undertaken in extensive ulcerating carcinoma one must be reasonably sure that the line of incision between the tail of the breast and the axilla will not pass through actively growing carcinoma, which was unfortunately the case in this patient.

CASE 7 (no. 251).—A. T., aged 39, a married, Jewish woman, born in Russia, had had five children, the first child being born thirteen years and the last nine years before the patient's admission to the Memorial Hospital. Lactation in all instances lasted about ten months with no mammary complication. There had been no history of trauma. Two months before admission the patient noticed a hard lump about the size of an egg in the left breast, which had steadily increased in size up to the time of admission. During this period she was conscious of a drawing sensation in and about the breast. On her own initiative she had applied salves and heat which she thought had caused some regression in the size of the tumor but had resulted in a blistering and reddening of the skin.

Examination on admission showed the patient to be in fair general nutrition. In the middle outer portion of the left breast was a poorly defined area of thickening 5 by 7 by 3 cm. There was moderate retraction of the nipple with some edema about it, and the nipple was fixed to the underlying breast tissue. Fixation of the skin was found over the tumor with an orange skin appearance over the outer and lower segment of the breast. There were several superficial blisters overlying the breast itself which was movable over deeper structures. A mass of axillary nodes 2 by 2½ cm. was palpable high in the left axilla. A roentgenogram of the chest showed no evidence of metastasis. There was some discussion in the breast clinic as to the operability of the case, but I felt that it was inoperable because of the high axillary nodes. Treatment was therefore begun immediately, and consisted of three low voltage roentgen cycles over the left breast and drainage areas with the following set-up: time, twenty-five minutes; milliamperes, 4; filters, 6.25 mm. of copper; spark gap, 10, and focal distance, 15. The last cycle was finished in March, 1925. Seven months after admission a small left supra-clavicular node was palpable, and a month later signs of metastasis were evident in the chest. The following month (nine months after admission) the mass in the breast had increased considerably in size and several nodules had appeared in the skin above the breast. A roentgenogram of the chest made at this time gave evidence of metastasis in both lungs. The patient's general condition was decidedly poorer than at the time of admission. One of the skin nodules removed was reported as infiltrating fibrocarcinoma. The patient finally left the Memorial Hospital, being transferred to another hospital where she died eleven months after admission to our service and one year and one month from the beginning of the symptoms. The disease had extended to the liver. One liter of fluid had been removed from the right side of the chest and there was extreme dyspnea before death.

As one reviews this case one may perhaps question the wisdom of having withheld radical operation when any question existed as to operability. My own conviction is, however, that in such a rapidly

progressive disease with high axillary nodes radical surgical intervention two months after the tumor was noted would have been of no avail.

Segment of the Breast Primarily Involved.—In 140 cases the left breast was the seat of disease; in 158 cases the right, and in 5 instances both breasts were involved. Dependable data are available in 140 cases concerning the site of the primary disease in the breast.

Figure 5 indicates the percentage of occurrences in various segments of the breast.

The most frequent site of the primary disease in carcinoma of the breast is the outer upper quadrant, 28 per cent occurring in this region,

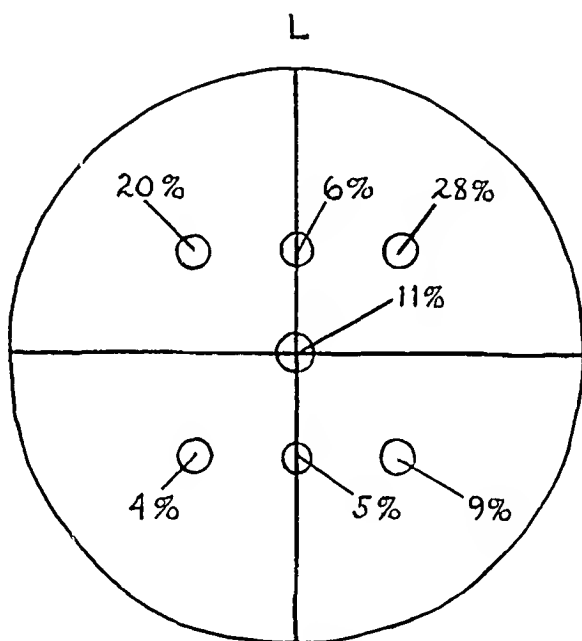


Fig. 5.—Segments of the breast in which disease occurred. The entire breast was affected in 17 per cent of the cases.

approximately one fourth of the entire group. If interference with drainage of the breast can be assigned as a cause for carcinoma, one would expect to find the primary disease more often in the upper outer quadrant, which extends far out toward the axilla, and drainage from this particular area is less effective than that from any other segment. In 20 per cent of the patients, the primary focus was in the upper inner quadrant. The most significant observation in these young women was a diffuse thickening of the whole breast as the initial symptom in 17 per cent of the cases, or approximately one sixth of the entire number. The primary focus was located with about equal frequency in the mid-portion of the breast and the lower outer quadrant.

Opinion has been unanimous that carcinoma of the breast involving the upper inner quadrant is more prone to furnish early metastasis in the chest than when the tumor invades other segments of the breast.

Figure 6 indicates the segments of the breast in which early pulmonary metastases are most prone to develop, and gives the percentage figures of occurrences in connection with each segment.

In the twenty-eight cases in which the upper inner quadrant of the breast was the primary site of disease, 21 per cent showed pulmonary metastasis as the first apparent extension of the disease, but 31 per cent of the sixteen patients in whom the middle segment of the breast was first involved showed the initial extension of the disease to the cavity of the chest.

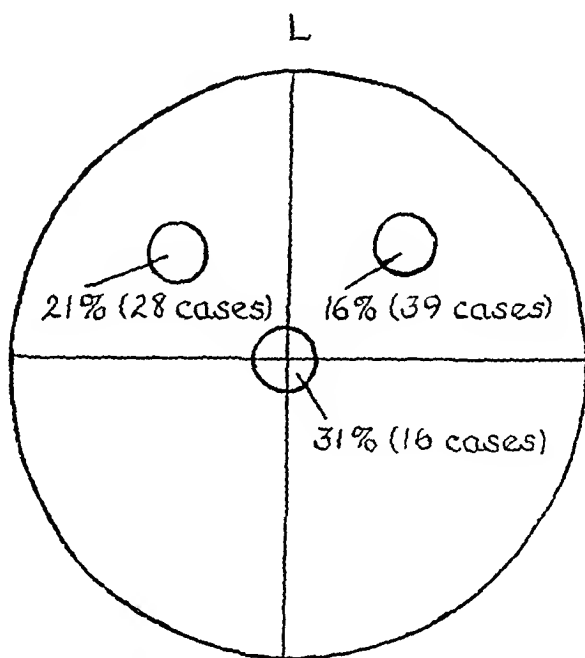


Fig. 6.—Percentage of pulmonary metastasis in various segments of the breast.

The groups of cases giving these percentages are not sufficiently large from which to draw too definite conclusions, but the menace of involvement of the upper inner quadrant of the breast, with the possibility of an extension of the disease to the intercostal lymphatics, is no more menacing, if as menacing, as when the middle segment of the breast is the site of disease.

PRIMARY OPERABLE CARCINOMA

Patients with primary operable cases, 243 in number, came to the clinic under one of four categories: (1) 44 patients with a primary operable setting, who were subjected to radical amputation at the Memorial Hospital; (2) 32 patients who received radical amputation in other hospitals in New York and were then referred to the clinic

for postoperative irradiation; (3) 115 patients who underwent radical amputation elsewhere, entering the clinic in recurrent phases of the disease, and (4) 52 patients with an operable setting who received some type of operation less extensive than radical amputation.

It is well to bear in mind that the 44 patients treated at the Memorial Hospital received uniformly a preoperative cycle of roentgen treatments before surgical intervention was attempted, and all received postoperative irradiation. The patients referred to the Memorial Hospital for irradiation after radical amputation elsewhere, received postoperative irradiation, no preoperative irradiation having been given. The 115 patients admitted in recurrent phases of the disease received neither preoperative nor postoperative irradiation, but were treated only for recurrent manifestations of the disease by irradiation methods.

Table 5 indicates the three year results following radical mastectomy in the three groups of patients mentioned. Figure 7 gives the percentage of patients alive and well at three month intervals during the entire three years. A study of table 5 suggests the conclusion that the

TABLE 5.—*Three Year Results Following Radical Mastectomy*

	Alive and Well	Per Cent	Alive and Recurrent	Dead	Total
Memorial Hospital patients.....	16	36	8	20	44
Referred for postoperative irradiation..	6	20	9	17	32
Recurrent on admission.....	8	7	31	76	115
Total.....	30	16	48	113	191

preoperative irradiation applied to the patients treated at the Memorial Hospital resulted in a higher percentage of success than did the deferred irradiation, for sixteen were alive and well at the end of three years. The fact that the criteria for the selection of patients for radical operation may vary considerably in the minds of different surgeons must, however, be taken into account. It seems fair to state that the criteria of operability are more sharply drawn at the Memorial Hospital than at other surgical clinics. There is, perhaps, a stronger tendency to scrutinize the patients carefully to be sure that a good operable setting exists. One might fairly assume that the better percentage in the group from the Memorial Hospital may be accounted for as much by the careful selection of cases as by the use of the preoperative cycle of roentgen treatments. Moreover, recent investigations carried on at the hospital strongly suggest that the preoperative cycle used as a measure of routine during the past ten years may be somewhat less effective than has been believed.

There is, however, no question that mammary cancer of radiosensitive type is definitely affected by the use of preoperative irradiation, and this evidence is found clinically in the regression in the size of the

tumor, and in the pathologic laboratory where histologic evidence abundantly demonstrates pronounced changes in the tissue in the irradiated tumors. These changes are more marked if a period of from three to five weeks is permitted to elapse before the radical amputation is undertaken. Further, inspection of table 5 shows that patients from the Memorial Hospital and those referred for postoperative irradiation give strikingly higher percentage figures for the three year results than do the patients admitted in recurrent phases of the disease. These better percentages may be explained on several grounds. Most of the patients referred for irradiation came from well organized surgical

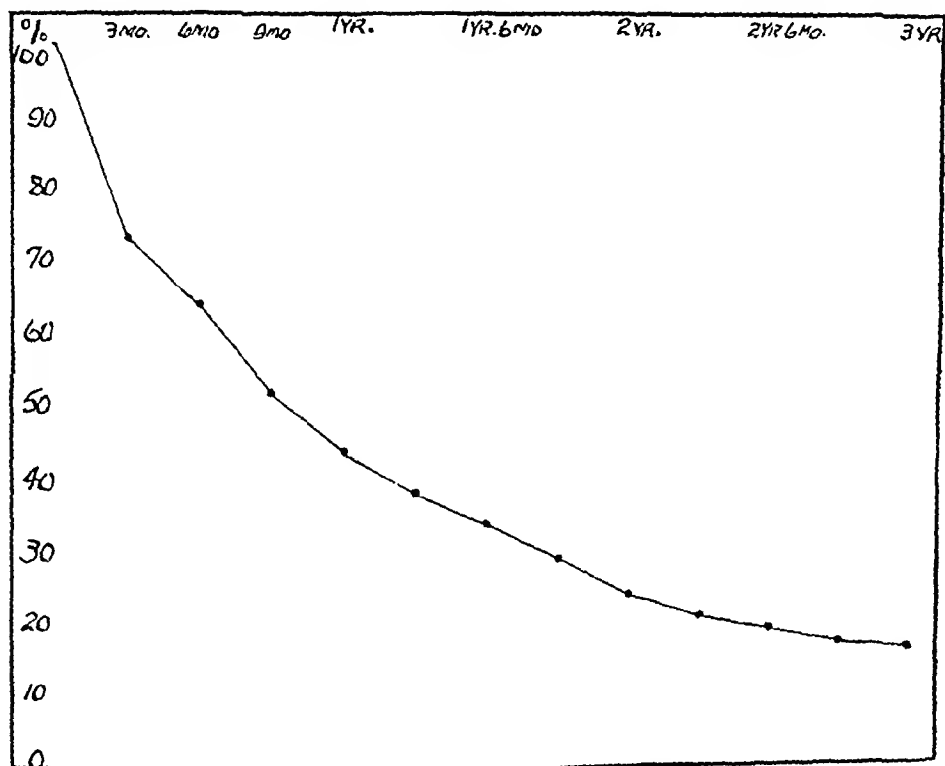


Fig. 7.—Percentage of 191 patients alive and well at intervals of three months for three years following radical mastectomy.

clinics in the city, where careful scrutiny of the patient is made and where the best type of surgery is done. Both of the first two groups, namely, the patients from the Memorial Hospital and those referred for postoperative irradiation, received radiation therapy following radical amputation, whereas those in recurrent phases of the disease did not. There seems little question that postoperative irradiation properly planned and efficiently given is of service in preventing recurrence and in causing the restraint of growth in tumor cells which may be left behind following surgical intervention. But, one factor must not be lost sight of, namely, that the surgeons whose patients finally found

their way into the Memorial Hospital clinic in recurrent phases of the disease undoubtedly had a certain number in whom the end-results were more favorable and who may have survived the three year period without evidence of recurrence. Without these additional facts from various surgeons, it is apparent that the figures for the recurrent group do not fairly represent the cross-section of the end-results in this group. With this in mind, the figure of 16 per cent for the three year results of radical amputation of mammary cancer in young patients is probably a lower figure than the correct one. The total of the Memorial Hospital patients and those referred for irradiation is seventy-six, twenty-two of whom were alive and well at the end of three years, a percentage figure of 30 per cent, which, we believe, probably more nearly represents the end-results to be expected.

Table 6 illustrates the three year results in the 191 patients subjected to radical amputation, when they are divided into five year age groups.

From a statistical standpoint, the number of patients occurring in the age groups of from 21 to 25 and from 26 to 30 years is too small

TABLE 6—*Three Year Results After Radical Mastectomy*

Age Period	Number of Patients	Percentage Alive and Well
21 to 25	6	17
26 to 30	24	17
31 to 35	58	12
36 to 40	10	17
Total	191	

to compare with the other two groups. The fifty-eight patients in the age group from 31 to 35 years and the significant facts that have been discovered explain the lower percentage of survivals in the age group from 31 to 35 years.

FACTORS INFLUENCING THREE YEAR END-RESULTS

Influence of Axillary Metastasis in Three Year End-Results.—Dependable data were available in sixty patients on the presence or absence of metastasis in the axillary nodes at the time of radical amputation. Of this number, axillary metastasis had been proved in forty-two patients at the time of operation, and at the end of three years but 10 per cent were alive and well, with no evidence of disease.

In the eighteen patients without involvement of the axillary lymph nodes, 67 per cent were alive and well three years following radical operation. These figures closely follow surgical experience with carcinoma of the breast without respect to age periods. In the patients in whom the nodes were involved, the average duration of life after operation was two years and six months, whereas those with no invasion of

the axilla gave an average duration of life after operation of five years and three months.

Influence of Lactating Breasts in Three-Year End-Results.—Experience at the Memorial Hospital has impressed us with the added menace to the patient with mammary carcinoma of a lactating breast. We have felt so certain of the seriousness of this clinical picture that in the presence of pregnancy we have uniformly advised therapeutic abortion before any attempt was made to deal surgically with the carcinoma of the breast. The present study confirms this conviction. In the series of 191 operable cases in which radical intervention was employed, a lactating breast was coexistent with the mammary carcinoma in 25. The end-results for this group of 25 women showed but 8 per cent alive and well without disease at the end of three years. When this figure is compared with the one already given, namely, 16 per cent for the entire group, it would seem fair to conclude that lactation coexistent

TABLE 7.—*Results of Limited Surgical Intervention in Operable Cases After Three Years*

Type of Operation	Number of Patients	Percentage Alive and Well
Limited radical	5	0
Local mastectomy	17	29
Local excision	18	22
Local excision and radical amputation after 2 weeks or more	12	12

with mammary cancer suggests a distinctly more menacing clinical picture and a poorer prognosis for the patient.

Three Year Results of Limited Surgical Intervention in Primary Operable Cases.—Fifty-two patients presenting a picture favorable for primary operation were subjected to surgical procedures less extensive than radical amputation. In some of these the breast was removed, and an incomplete axillary dissection done without any attempt to remove the pectoral muscles. Surgical intervention of this type, for want of a better name, we have called "limited radical." Other patients underwent local mastectomy only, a local excision of the tumor itself or a local excision, radical intervention being done more than two weeks after the preliminary operation. Table 7 gives the results in this group of cases at the end of three years.

None of the patients subjected to a "limited radical" operation survived the three year period. The reasons for employing such a surgical procedure is not always apparent. It seems probable that either poor surgical judgment determined the type of operation to be performed or that the clinical setting was too advanced to expect much from radical surgical intervention. Whatever the reasons for adopting this method, the end-results demonstrate that "limited radical" operations are unwise

in dealing with mammary cancer. Local mastectomy alone was performed 17 times, with a much higher percentage of patients alive and well than that obtained for the 191 patients subjected to radical amputation, but lower than that, 36 per cent, for the patients from the Memorial Hospital. Local mastectomy was chosen, apparently, because of the clinical setting, for in many instances a positive diagnosis of cancer was not made prior to the time of operation. Moreover, many of these patients had no palpable axillary nodes, which may have influenced the surgeon in his judgment toward local mastectomy; it is also possible that many of these cases were of lower grades of malignancy. In general, the procedure is to be condemned as an alternative for radical surgical intervention.

Local excision was performed in eighteen cases, and there is little doubt that in most of them the preoperative diagnosis was that of benign tumor. The fact that 22 per cent of the patients survived the three year period suggests that many of the tumors were of a low grade of malignancy.

But 12 per cent of the twelve patients in whom local excision was followed by radical amputation after two weeks survived the three year period. The experience of many surgeons, especially that of Peck and White,³ has strongly suggested that local excision followed shortly by radical mastectomy yields as good end-results as radical amputation alone, but a delay in performing the latter adds to the patient's hazards.

The results of these types of limited surgical intervention in the fifty-two cases have been recorded for completeness, but any surgical procedure less than a radical amputation in a group of younger women should be condemned and considered poor surgical practice.

RECURRENCE AFTER RADICAL MASTECTOMY

A study of the rapidity of recurrence shows several interesting facts. Table 8 indicates the number of patients of the entire series of 191 in whom the disease recurred after a postoperative interval of three months and one year.

Inspection of table 8 shows the rapidity of recurrence in all of the groups but especially in those coming to the clinic in recurrent phases of the disease. In more than one third of these patients the disease recurred within three months, and in approximately two thirds it had recurred within the first postoperative year. The percentages of recurrences in the Memorial Hospital patients and in those referred to us for postoperative irradiation are fairly comparable and should represent what one might reasonably expect to be the result of radical amputation

3. Peck, C. H., and White, W. C.: Tumors of the Breast, Benign and Malignant, *Ann. Surg.* **75**:641, 1922.

in well selected operable cases in young women. When the entire group of 191 patients is considered, it will be seen that the disease recurred in a little over one fourth of the patients within the first three months and in exactly one half within the first year.

Table 9 represents the result of the analysis of all the cases recurring within three months.

The inevitable conclusion to be drawn from a study of these cases of rapid recurrence is that either the patients were unsuited for radical surgical intervention, that poor surgical technic was employed in the radical amputation, or that both factors combined to give the poor end-result.

One should scrutinize most carefully the whole clinical setting in a case of mammary cancer in a young woman, and only after most care-

TABLE 8.—*Recurrence of Disease After Radical Amputation*

	In Three Months		In One Year	
	Patients	Per Cent	Patients	Per Cent
Memorial Hospital patients.....	5	11	15	33
Referred for postoperative irradiation.....	4	13	9	28
Recurrent on admission.....	42	36	72	63
Total.....	51	27	96	50

TABLE 9.—*Rapid Recurrence After Radical Mastectomy*

Immediate	5
Within 1 month.....	17
Within 2 months.....	13
Within 3 months.....	16
Total.....	51 (27%)

ful physical examination should the surgeon reach a decision as to the favorable condition of the patient for operation.

Concerning the surgical technic, one is impressed with the tendency to perform radical amputation with too much speed and too little care, the operation often being a traumatizing procedure. Unless every detail of surgical technic is carefully thought out and put into practice, early recurrence will surely follow, and the study of the present series of cases proves that the hazard of early recurrence is present to a much larger degree in young than it is in older women.

The following history indicates the lack of wisdom in operating on a younger woman in whom the condition was clearly inoperable from the outset.

CASE 8 (no. 260).—S. A., aged 40, a white woman, married, was born in Poland. She had had seven previous lactations, the first seventeen years and the last one year before admission. She usually nursed her babies for eighteen months. Two weeks before she entered the Memorial Hospital she noticed that the whole right

breast was becoming swollen. Shortly afterward the breast felt hard. The swelling increased rapidly, and at this time the patient noticed sticking pains and a burning sensation in the breast.

Physical examination showed the patient to be in fair general nutrition. The entire right breast was enlarged and completely occupied by a tumor. There was marked retraction of the nipple, which was edematous, and the lower segment of the breast showed a definite pigskin appearance. There was fixation of the skin to the underlying mammary tissue, and the surface of the breast was red, with irregular multiple nodules over it. There was a large chain of hard nodes in the right axilla and a questionable node in the right supraclavicular region. A roentgenogram of the chest was made and was negative for metastasis. A diagnosis of inoperable carcinoma was made, and it was decided that the patient should be treated entirely by irradiation. One high voltage cycle of roentgen ray was given

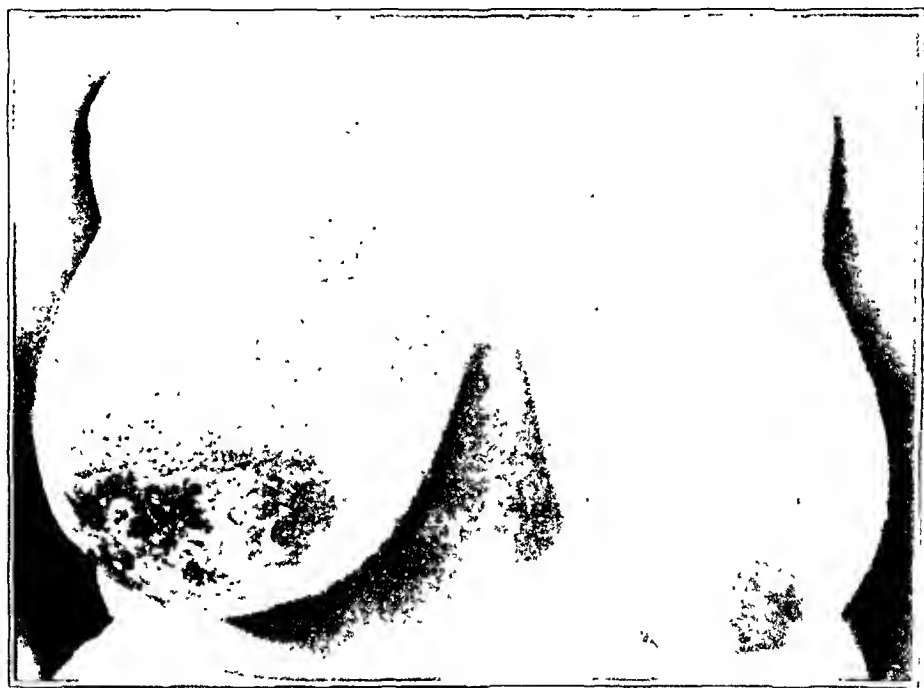


Fig. 8 (case 260).—Photograph shows extensive pigskin appearance of the right breast.

over the right breast and drainage areas with the following set-up: time, six minutes; milliamperes, 4; filter, 0.5 mm. of copper; spark gap, 90 cm., at a focal distance of 50 cm. The patient left the clinic, and two months later a radical amputation was performed.

The pathologic report of the tissue removed showed the case to be one of infiltrating carcinoma simplex, with large opaque cells. Two months after the operation a letter from the patient stated that she was "home now, but not doing the way I expected to be. I believe it's starting in my other breast now, because today it's all inflamed and very feverish. Have a pain in it and in the pit of my arm."

During this time she was still going to the hospital for dressings, the incision not having healed. Through the wound of operation a fungating tumor formed, and, although some attempt was made to control the disease by further irradiation, the whole process was rapidly progressive, with wide dissemination, and the patient died five months after the operation and seven months after the beginning of symptoms.

One hundred and forty-three patients are available in whom five year end-results may be tabulated. Figure 9 gives the percentage of those alive and well at intervals of six months during the entire five years.

PATHOLOGIC REPORT

Gross material, microscopic slides or histologic reports from other hospitals were obtained in 169 of 303 patients.

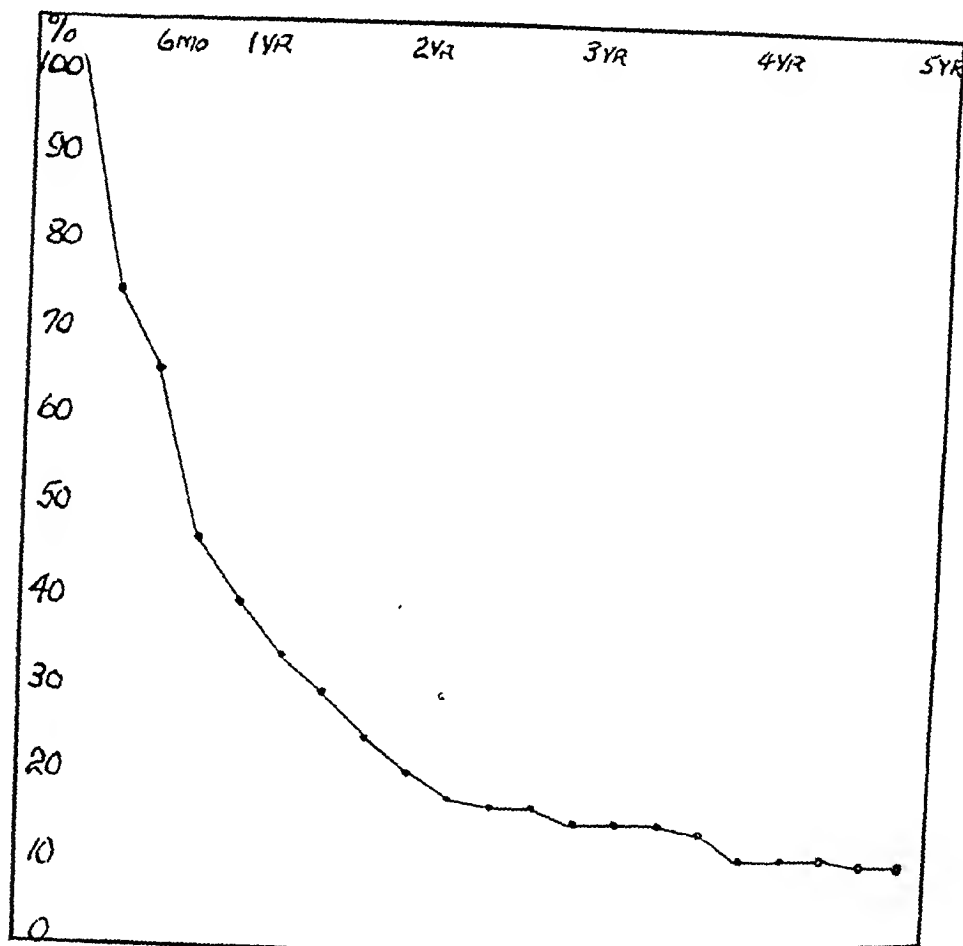


Fig. 9.—Percentage of 143 patients alive and well at the end of five years following radical mastectomy.

From the Memorial Hospital, tissue was available for study in all of the forty-four primary operable cases and in twenty-eight of the sixty primary inoperable cases. In the group referred to us by other New York hospitals for postoperative irradiation, slides were available in the majority of instances, and in practically all of the other cases of this group, histologic reports were sent to the clinic. Few microscopic slides were obtained of the cases in the recurrent group, but in approximately one half of these, histologic reports were obtained.

A wide variation exists in the minds of different pathologists as to the histologic types of mammary cancer. Therefore, a tabulation of these 169 patients would appear to us to be of little value from the standpoint of accurate information on the histology of this disease, so we have excluded it from this report.

Tissue for histologic study in the laboratory at the Memorial Hospital was available in seventy of the patients. In eight instances the histologic material obtained from sources outside the hospital was of such a character that it was impossible to determine the type of the disease. Table 10 indicates the types encountered in the remaining sixty-two patients. Inspection of this table shows that forty-two cases (or slightly more than two thirds) were of the duct carcinoma type; ten of these were of the small cell variety, which has been considered in the laboratory a particularly menacing form of the disease with a

TABLE 10.—*Histologic Types of Sixty-Two Patients*

	Number of Patients	Total
Adenocarcinoma		
Bulky adenocarcinoma	12	
Gelatinous adenocarcinoma	2	
Papillary adenocarcinoma	2	16
Duct carcinoma		
Small cell duct carcinoma.....	10	
Infiltrating duct carcinoma.....	27	
Large cell duct carcinoma.....	1	
Duct carcinoma, sweat gland type.....	2	
Intraductal papillary carcinoma.....	2	42
Infiltrating tubular carcinoma.....	3	3
Carcinoma simplex	1	1

tendency to disseminate early and widely; twenty-seven others were classified as infiltrating duct carcinoma. This form of the disease, although less active than the small cell type, is nevertheless serious. Of the sixteen adenocarcinomas, twelve were classified as of the bulky adenocarcinoma type, which early in its course is not a highly malignant tumor of the breast; later, as the disease progresses and nodes become involved, it shows infiltrative qualities, and in this stage presents a serious form of the disease. There were but two cases of gelatinous adenocarcinoma, a tumor generally recognized as of low grade malignancy. Two cases of papillary adenocarcinoma and two additional ones of intraductal papillary carcinoma were also encountered, and both of these lesions are relatively benign. The histologic survey demonstrated that but six cases of the entire group were of low grade malignancy.

Histologic grading was done in forty-three of the patients, placing six in grade 1, twenty-six in grade 2 and eleven in grade 3. The thirty-seven patients falling into grades 2 and 3 constituted 86 per cent of the forty-three cases studied.

In this series fifty-two of the histologic slides studied with respect to radiosensitivity showed that thirty-six could be classified as radio-resistant and but sixteen as radiosensitive. An attempt to determine the quality of radiosensitivity or radioresistance in mammary cancer is attended with considerable difficulty. It seems probable that the reaction of tumor tissue to irradiation depends as much on such factors as the supply and abundance of the blood and the character of the stroma as on the inherent qualities in the cancer cell itself. The small cell duct carcinomas are generally regarded as radiosensitive, as are also some of the papillary adenocarcinomas. If the tumor is highly cellular, with little stroma, one is inclined to consider it as sensitive to irradiation. One cannot conclude that a high degree of malignancy is always associated with radiosensitivity, for some of the highly malignant forms of mammary cancer are comparatively radioresistant.

Histologic studies were made of a similar number of patients in the age group of 60 years and over, in order to determine if any marked difference existed in the histologic appearance as compared with that of the younger patients. This study revealed that more tumors of an adenocarcinomatous type and fewer instances of small cell duct carcinoma were apt to be encountered in the older women. No marked difference could be discovered in these two divergent age groups with respect to the quality of radiosensitivity.

TREATMENT

The first step in the appropriate treatment of a young woman suffering from a tumor of the breast is a complete physical examination to establish a correct preoperative diagnosis. If a diagnosis of mammary cancer is made, or is strongly suspected, roentgenograms of the chest and osseous system should be studied for metastases. If the breast is largely occupied by tumor tissue, if the axillary nodes are extensively invaded or if there are one or more cutaneous nodules overlying the tumor in the breast, the case should be considered inoperable. On the other hand, if there is a small or moderate-sized tumor in the breast, without invasion of the axillary nodes or with but one or two palpable nodes, radical amputation would seem the proper course to follow. Before surgical intervention is undertaken, the patient should be treated adequately by irradiation, a cycle of high voltage roentgen treatments being given over the breast and drainage areas. If the tumor is radiosensitive, regression in size will follow within three or four

weeks. No benign tumor of the mammary gland responds in this way to irradiation. If the tumor is of radioresistant type, the degree of regression will be less marked or there may be no diminution in size.

Recent investigations at the Memorial Hospital have shown that devitalization of mammary cancer requires the equivalent of ten full erythema doses that can be delivered by high voltage roentgen rays to the most distant part of the tumor. During the past few months, I have attempted to deliver this dose by supplementing the high voltage roentgen cycle with interstitial radiation, furnished by the insertion of gold radon seeds directly into the mass. The tumors are carefully measured and their exact size and shape plotted. Through the cooperation of the physics department, we have been able to obtain information as to the exact amount of gold radon seeds which must be implanted to bring the total dosage up to an equivalent of ten erythema doses. This amount is apparently sufficient to devitalize the most radioresistant cancer of the breast. The axilla is treated in a similar manner. Radical amputation is performed from four to five weeks after the insertion of the radium, and histologic studies revealed in many instances almost complete devitalization of the tumor. Time will show whether the end-results following this procedure justify the method.

Following the operation, postoperative irradiation is for the present being withheld, because it seems wise to determine the adequacy of pre-operative irradiation.

A similar procedure is followed in the patients in whom the disease has passed beyond the stage of operability. If an ulcerating mass is present, a palliative mastectomy is often done one or two months after the completion of adequate irradiation. This operation should never be attempted if tumor tissue stretches continuously from the breast up to and into the axilla.

The radium element pack may be substituted for high voltage roentgen rays if the process appears to be sharply defined, and we expect a more pronounced regression following its use than when high voltage roentgen rays are employed.

A continuous follow-up in this group is even more essential than in women of older age periods.

SUMMARY

Cancer of the breast in young women is a much more menacing disease than it is in midlife or in old age. The course is often dramatic in its rapidity, almost simulating an infectious process. When the first symptom is a diffuse enlargement of the breast, a redness overlying the mammary gland or pain, surgical intervention is futile. A more careful examination of younger as compared to older women must be exercised before radical operation is undertaken. Early recurrence is

more frequent in younger than in older women, and indicates either a poorly chosen case for surgical intervention or poor surgical technic or both. In many of these patients, reliance must be placed entirely on radiation therapy. In well chosen cases, well planned adequate irradiation combined with a carefully performed radical amputation yields the best results.

ESOPHAGEAL FISTULA IN THE EXPERIMENTAL ANIMAL *

T. S. WILDER, M.D.

AND

JOSEPH STOKES, JR., M.D.

PHILADELPHIA

It has never been entirely clear that a failure of saliva to reach the stomach, owing to complete stenosis or to fistula of the esophagus, is of itself incompatible with normal growth, although such a possibility has been suggested by more than one author. Chevalier Jackson¹ noted the clinical benefit to patients with esophageal stenosis of their adding saliva to their food by preliminary chewing. In a personal communication Prof. A. J. Carlson mentioned a child with complete obstruction of the esophagus who was undoubtedly helped by a regimen of mastication of food before its introduction into the gastrostomy tube by which she was fed. Carlson ascribed the rapid gain in weight which he observed mainly to the secretion of gastric juice accompanying appetite and the chewing reflex, and questioned the importance of the actual presence of saliva in the food. Likewise, Prof. A. C. Ivy wrote us that he produced complete esophageal fistulas in dogs and maintained them for over a year by careful gastrostomy feeding accompanied by sham drinking. It seems probable, as Ivy suggested, that the benefit from mastication of food may lie, not in the saliva, but in a "cephalic conditioning of the digestive organs for both the motor and secretory work they are about to perform."

It is, of course, possible that continuous loss of salivary secretions from the body may cause a depletion of such mineral substances as sodium, calcium, potassium, chloride, phosphate, etc., contained in the saliva. Gamble and Ross² showed that pyloric obstruction may reduce the total chlorides of the body by one-third, with fatal results. The experiments of certain other workers suggested that a possibly analogous effect may be produced by obstruction higher in the intestinal tract than the pylorus—that is to say, at the cardia or even in the midesophagus. Haden and Orr³ produced esophageal obstruction in dogs with rapidly

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* From the Laboratory of Research Surgery and the Department of Pediatrics, University of Pennsylvania Medical School.

1. Jackson, Chevalier: *Arch. Pediat.* **40**:324, 1923.

2. Gamble, J. L., and Ross, S. G.: *J. Clin. Investigation* **1**:403, 1925.

3. Haden, R. L., and Orr, T. G.: *J. Exper. Med.* **38**:477, 1923.

fatal results, their chemical studies showing a decrease in the chlorides of the plasma and an increase in nonprotein nitrogen. The explanation offered by these authors presupposed the rapid formation in the obstructed esophagus of a toxin which induced a fatal toxemia. With this hypothesis Wangensteen and Chunn⁴ disagreed. They, too, reported a rapid lethal outcome following the operation, but felt that the administration of saline solution subcutaneously prolonged life by replacing salt and water that had been lost. The authors reached this conclusion from the fact that they had observed a decrease in the chlorides of the plasma and from noting the urinary excretion of salt and water. They stated that "on the same basis of loss of fluid and fixed base from the body, some alteration in the permeability of tissue is necessary to explain the death of an animal with esophageal obstruction, or a rabbit with duodenal obstruction that does not vomit." Later, the force of this argument was weakened when Gamble and McIver⁵ explained the apparently anomalous behavior of the rabbit by showing that following pyloric obstruction chlorides accumulate in the stomach of this animal to such an extent that the body as a whole is depleted fully as much as though the gastric secretions had been vomited. In a recent paper White and Fender⁶ showed that the retained secretions above a jejunal obstruction, when removed and reinjected below the obstruction, prolong life as efficiently as does saline solution, with no signs of toxicity.

Further work of an experimental nature by Andrus and Donnelly⁷ recently appeared. These authors reported the death of animals with complete esophageal obstruction in an average of fifty-three hours; similarly, animals with complete esophageal fistula died in an average of seventy-three hours. In their experiments the administration of solutions containing sodium chloride or sodium chloride plus sodium bicarbonate appeared valueless. These authors stated that the cause of death is not clear and intimated that the loss of saliva may play an important rôle in the lethal outcome. Although this may be considered as a possibility, it is difficult to imagine a chemical mechanism to explain it, whereas loss of chlorides from the stomach in pyloric obstruction has a perfectly obvious physiologic implication.

4. Wangensteen, O. H., and Chunn, S. S.: *Studies in Intestinal Obstruction: III. Simple Obstruction; a Study of the Cause of Death in Mechanical Obstruction of the Upper Part of the Intestine*, Arch. Surg. **16**:1242 (June) 1928.

5. Gamble, J. L., and McIver, A.: *J. Clin. Investigation* **1**:531, 1925.

6. White, J. C., and Fender, F. A.: *The Cause of Death in Uncomplicated High Intestinal Obstruction: Experimental Evidence to Show that Death Is Due Not to Toxemia, But to Loss of Digestive Fluids and Salts*, Arch. Surg. **20**:897 (June) 1930.

7. Andrus, W. de W., and Donnelly, J. I.: *Effects of Certain Operations on the Esophagus of the Dog, Including Esophageal Obstruction and Complete Esophageal Fistula*, Arch. Surg. **20**:1 (Jan.) 1930.

Indeed, if the deaths observed could be explained by the loss of chemical substances from the body, pyloric obstruction should be more rapidly fatal than esophageal obstruction instead of less so, since saliva is lost in both instances and the gastric secretion is lost only in the former.

The feeling is now general that no satisfactory explanation for the rapid deaths observed in experimental esophageal obstruction or in fistula has been advanced. It is possible, as Ivy suggested, that neither toxemia nor loss of saliva is responsible, but rather some kind of obscure "reflex or pulmonary disturbance." It is possible that technical difficulties in producing low esophageal obstruction and fistula may play a part in the high mortality previously reported.

Whether or not one regards the rapid loss of salivary secretions as serious, there is evidence that the mere lack of saliva is not particularly harmful. In the first place, there are reports of at least two cases of congenital absence of all the salivary glands; one, cited by Blackmar,⁸ occurred in a boy, 11 years old, and another, cited by Ramsey,⁹ in a girl, aged 5, whose father was similarly afflicted. On the experimental side, Hemmeter¹⁰ concluded from his work that extirpation of the salivary glands in dogs reduces gastric secretion, whereas Swanson¹¹ in repeating the work failed to agree with this observation.

There are apparently no data as to the degree of retardation in growth of the young animal that may be expected either from lack or from loss of saliva. Although this is a slightly different aspect of the problem from that discussed in the preceding paragraphs, it has been of chief interest to us because of its bearing on a case occurring in a 10 year old patient of Dr. Chevalier Jackson's, which it has been our privilege to study. This case, one of complete stenosis of the esophagus of eight years' duration, reported by us elsewhere, need be mentioned only in passing. So extreme was the child's malnutrition when we first saw her that we were almost willing to concede that her daily loss of saliva was perhaps largely to blame for her condition. Somewhat to our surprise, we found that as soon as we adapted the quality, consistency and caloric value of the patient's diet to the requirements of gastrostomy feeding, a remarkable change occurred. The weight increased from 37 to 65 pounds (16.8 to 29.5 Kg.) in ten months. During the last three months of that period the child was not permitted to mix any saliva with her food, a change that caused no slacking in her rapid rate of growth (a steady 3 pounds [1.4 Kg.] per month). More-

8. Blackmar, F. B.: *Am. J. Ophth.* **8**:139, 1925.

9. Ramsey, W. R.: *A Case of Hereditary Congenital Absence of the Salivary Glands*, *Am. J. Dis. Child.* **28**:440 (Oct.) 1924.

10. Hemmeter, J. C.: *Science* **25**:473, 1907; *Tr. Am. Gastro-Enterol. A.*, **11**:5, 1908.

11. Swanson, A. M.: *Am. J. Physiol.* **43**:205, 1917.

over, there was no anemia, and roentgenologic examination of the bones showed normal structure. Our tentative conclusion was that in this instance the loss of saliva had not been intimately associated with the retarded growth and development.

EXPERIMENTS

Since similar cases in man are rare, we decided to attempt to duplicate the condition in a litter of month old pigs, these being in some ways more suitable for comparison than are the more common laboratory animals. A three-stage operation was performed by Dr. I. S. Ravdin in the following manner:

With the animal under sodium amytal anesthesia, a 3 inch (7.6 cm.) incision was made just behind the posterior border of the lower end of the sternocleidomastoid muscle. The esophagus was freed for about 3 inches (7.6 cm.) and brought to the surface. Next, the midportion of the original wound was closed, leaving a portion of the esophagus external to the skin. Petrolatum and a gauze dressing were applied, and after a few hours the pig was allowed to drink small amounts of fluid. There was evidently some difficulty in swallowing, since the animals operated on voluntarily limited their intake of food to a fraction of what it had been previously. In from one to four days following the operation, an opening was made in the esophagus with a cautery, and liquid food was introduced into the stomach at regular intervals. Later the esophagus was divided, and we then had two esophageal fistulas: from the upper one saliva flowed, and into the lower one food and water were introduced.

Control animals were fed the same diet per kilogram of body weight as the animals operated on received by tube three times a day. The food was liquid, with milk as a basis, to which were added dextrose syrup, cod liver oil, tomato juice and vitavose to supply calories and vitamins.

Two groups of animals were used. The first group consisted of nine pigs, of which one, born late in December, was operated on on January 23. Of the remaining eight, born in one litter on January 4, six were subjected to operation (four on February 3 and two on March 5). In no instance did we have a sudden death following operation, the shortest period of survival being five days in a pig that had had diarrhea. A second pig died of mediastinitis nine days after operation, a third of abscess of the lung and pericarditis in fourteen days, and a fourth in twenty-six days of porcine scabies, which also killed one of the controls (not operated on) ten days later.

Four animals then remained, and of these one died on the hundredth day of a ruptured stomach, produced, we supposed, by the tip of the tube used for feeding. The other two animals operated on were killed on the hundred and thirty-second day when they had become too large for convenient handling.

Figure 1 illustrates the excellent gains in weight made by the three last mentioned animals despite their esophageal fistulas. To be sure, an even better gain was made by the control, but this is not surprising in view of the handicaps the animals operated on were under because of the abnormal method of feeding and the loss of fluid as saliva through the upper fistula. We experienced, indeed, considerable difficulty with

the feeding by tube, owing to a tendency on the part of the animals to regurgitate some of the food. Moreover, unless food was given very slowly, there were symptoms of painful distention of the stomach, due perhaps to absence of reflex relaxation. Undoubtedly, the psychic disadvantages of feeding by tube militated against the complete success of this procedure in the animals operated on.

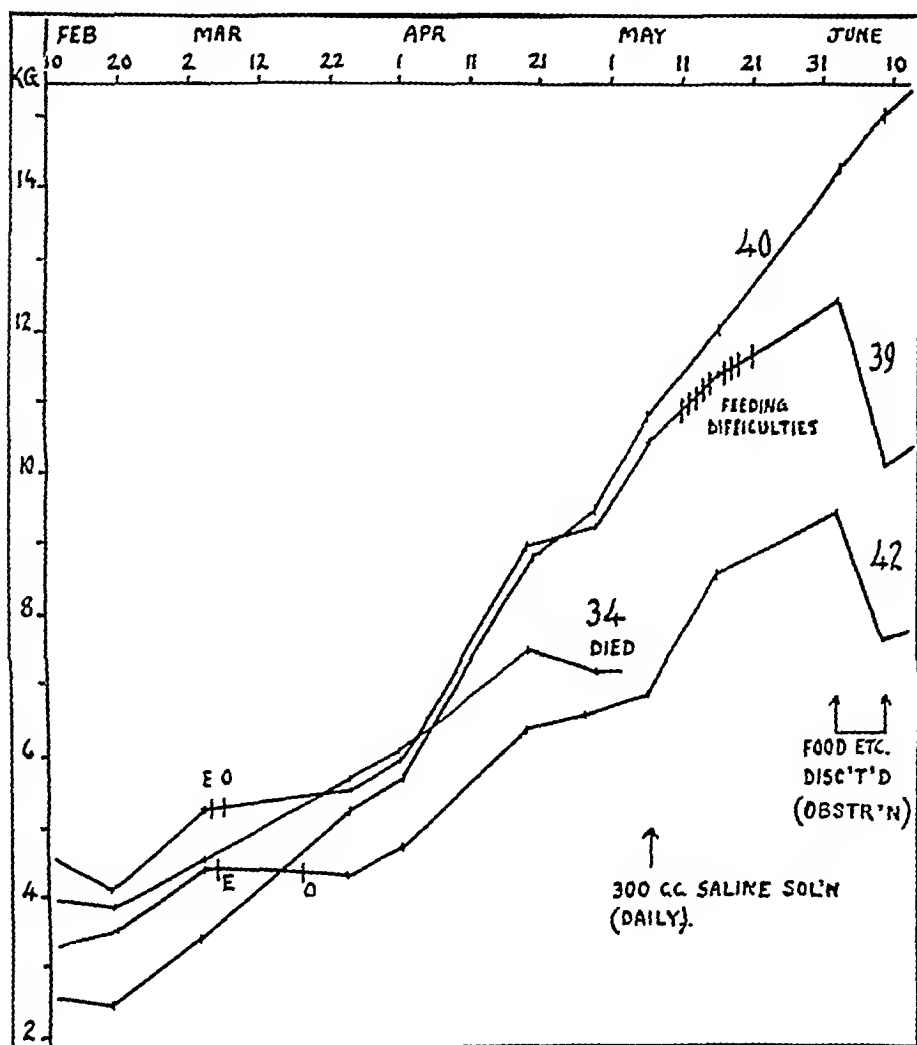


Fig. 1.—Weight curves of three pigs with experimental esophageal fistula and of one control (no. 40). Pig 34 was operated on on Jan. 23, 1930, and pigs 39 and 42 on the dates indicated by *E*, following which the esophagus was opened on the dates indicated by *O*. The esophagus was completely divided within seventy-two hours from the time it was opened.

Loss of saliva from the fistulas might have affected the pigs operated on unfavorably in two ways: (1) by depriving them of whatever digestive value this secretion may possess, and (2) by depleting the body of fluids and certain mineral ions. An estimate of the loss sustained is difficult to make, but in view of the fact that the salivary secretion in

man is reputed to be from 1,000 to 3,000 cc. daily, it is probable that the pigs lost from 200 to 500 cc. Certainly there was marked drainage from the salivary fistulas, a fact appreciated by the control animal, which developed the habit of sucking at the necks of his companions. It was to compensate for the salivary loss that we commenced giving a daily ration (300 cc.) of 8.9 per cent saline solution to the pigs when they were 3 months old (fig. 1). Apparently this did not exert a noticeable effect on the weight curves during the ensuing two months.

Shortly before we were ready to terminate the experiment we caused complete obstruction of the esophagus of the two pigs operated

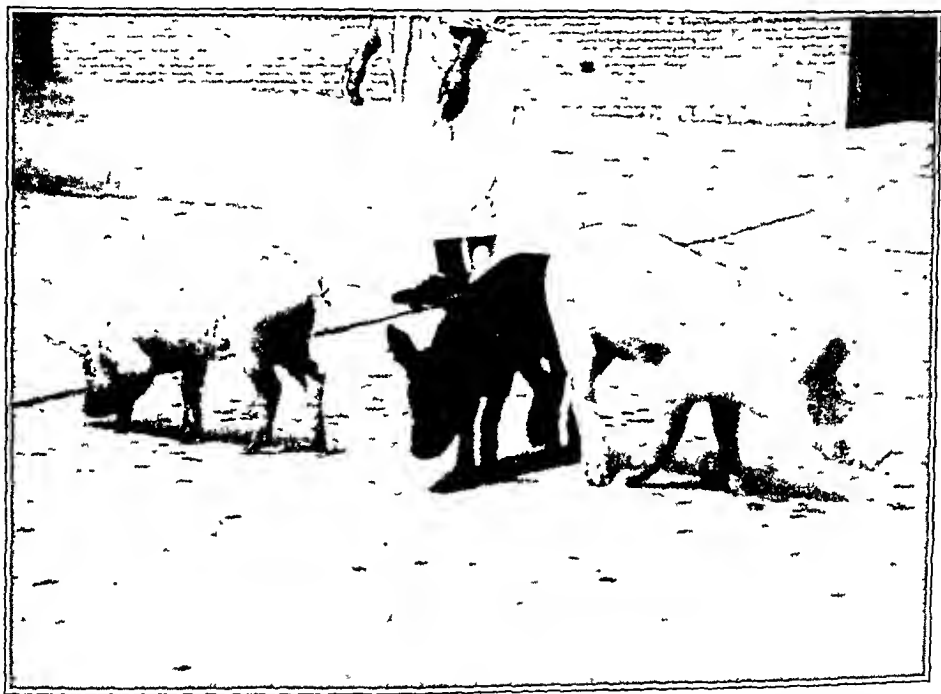


Fig. 2.—Three pigs of the first litter: to the left, pig 40 (control); at the center, pig 42 (fistula), and at the right, pig 39 (fistula).

on that remained. This was maintained for ninety-six hours, the animals receiving no food or water. The obstruction was then removed, but food and water were withheld for another twenty-four hours. The animals were then fed as usual, and in three weeks one had gained over 1.5 Kg. Both were in excellent condition, but the second pig did not gain much weight, owing to increased regurgitation of food. Our conclusion was that the four days of acute obstruction had caused little disturbance aside from that of temporary starvation and dehydration.

A second litter (five pigs born on May 1, 1930) was obtained on May 28, and two of them were subjected to operation on June 6. Our object was to duplicate the previous experiment with a single modification, the addition of saline solution, from the beginning, to the

diet of the animals operated on. The only other differences were that the second litter was somewhat heavier than the first and benefited also from the improvement in our technic resulting from our experience in the postoperative management of the first litter.

The results were similar to those previously obtained, except that neither of the animals operated on and none of the controls died. The gain in weight following operation was more immediate and there were not the difficulties in feeding encountered in the previous experiment. The table lists the changes in weight.

The animals were slaughtered thirty-eight days after operation, as we felt that there was no object in carrying the experiment any further. It is worth mentioning, perhaps, that in the eighteen days between June

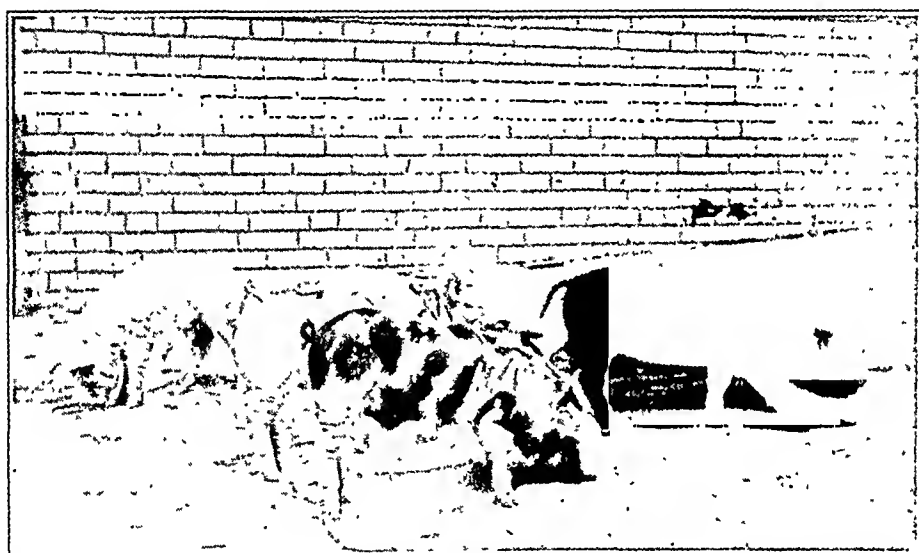


Fig. 3.—The second litter one week after the completion of the fistulas.

Changes in Weight in Pigs Subjected to Experimental Esophageal Fistula

Date	Pig 66 Kg.	Pig 67 Kg.	Pig 68 Kg.	Pig 69 Kg.	Pig 70 Kg.
June 2.....	6.1	6.5	7.0	7.0	6.2
June 6.....	Control	Operated on	Operated on	Control	Control
June 7.....	...	Operated on	Operated on		
June 9.....	6.9	5.9	7.0	7.4	7.0
June 27....	8.8	7.3	8.3	9.2	9.1
July 14.....	9.4	8.2	8.5	10.0	10.3
July 14.....		(All animals slaughtered)			

9 and June 27 the animals operated on added 22 per cent to their weight and the controls 25 per cent, practically identical amounts. These figures may, however, favor the animals operated on to some extent, since part of the excellent gain in at least one animal may have been merely replacement of body fluids lost in connection with the operations of June 6 and 7.

COMMENT

We attempted to investigate the effect of complete loss of saliva on the growth of a young animal (the pig). Somewhat to our surprise, our results appear to indicate that an esophageal fistula is not in itself particularly inimical to normal growth. The use of a three-stage operation probably contributed materially to the ease with which experimental fistulas were secured and maintained in our animals. We did not encounter instances of rapid death such as had been reported by various authors in the case of dogs. The explanation may hinge either on our use of a different animal or on our use of a different operation. So far as we have shown that loss of saliva is comparatively safe, we have perhaps helped to rule out that factor as an element in the lethal outcome of such operations on dogs. As to what other factors may be at work we have no data. Even in our animals there were periods of choking and cyanosis, which resulted either from aspiration or, as has been suggested by Ivy, from some type of reflex pulmonary disturbance. Possibly, in dogs this particular hazard is greater than in pigs. It would, perhaps, be interesting to attempt the three-stage procedure in dogs.

Chemical studies of the plasma would have been difficult to obtain. Moreover, we felt them to be superfluous in our experiments, as soon as it became apparent that the pigs did not die. In the rapidly growing young animal one would certainly not anticipate marked deviations from normal.

As to the clinical application of the work that we have outlined, we can suggest only that patients with esophageal obstruction or fistula require primarily individual dietetic care with particular attention to adequate calories in liquid form. The psychic benefit of preliminary mastication of food should not be overlooked as a measure of considerable secondary value.

SUMMARY

1. In month old pigs, experimentally produced esophageal fistulas causing complete loss of saliva did not materially interfere with normal growth.

2. The operations were performed in three stages, without the complication of rapid death that had been reported in the case of dogs.

3. Apparently loss of saliva is less harmful, and proper dietary management more important, in these conditions than has been supposed.

PARTIAL CHOLECYSTECTOMY *

W. L. ESTES, JR., M.D.

BETHLEHEM, PA.

From the reports of the end-results of operations on the gallbladder, cholecystectomy has been shown to be the operation of choice in disease of the gallbladder with or without stones.

In patients with acute infections of the gallbladder, frequently bad risks, cholecystectomy is often technically difficult, and cholecystostomy is resorted to because of the ease and rapidity with which it may be executed, as well as the fact that drainage of the biliary tract may be indicated, and it affords a ready means of drainage of the biliary ducts. In from 25 to 50 per cent of the cases, this measure is only palliative, and cholecystectomy is later necessary because of persistent infection in the gallbladder with recurrent symptoms, the formation of stones or a biliary fistula. The ideal operation for even acute cholecystitis, provided it were safe, would be cholecystectomy or an operation that would destroy or remove the gallbladder, provide drainage of the bile passages and avoid the likelihood of a second operation. When, however, disease of the gallbladder is complicated by marked pancreatitis, diffuse cholangitis or involvement of the common duct, the use of the gallbladder for drainage may outweigh the necessity for its extirpation, or it may be needed for a later cholecystenterostomy. Likewise, cholecystectomy is especially dangerous in the presence of jaundice, because of the likelihood of hemorrhage from the gallbladder fossa or liver, which may be difficult to control. Cholecystostomy may therefore be an operation of necessity or an operation of choice. In the cases in which cholecystostomy is used of necessity, cholecystectomy would be preferable, but it is abandoned because (1) drainage is indicated, or (2) it is technically too difficult or impossible.

In 1923, in a case of multiple stones in the common duct and gallbladder with obstructive jaundice, I observed Dr. W. J. Mayo, instead of performing a cholecystectomy or the usual cholecystostomy, split the gallbladder from fundus to ampulla, remove the stones, and conclude by holding the gallbladder open its entire extent by properly placed drains.

A short time later, I was confronted by a case of gangrenous cholecystitis with stones in which complete cholecystectomy was definitely indicated; because of inflammatory induration about the cystic

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* Read in part at the Meeting of the Southern Surgical Society, Dec. 11, 1925.

duct, however, this method seemed technically inadvisable and probably dangerous. I therefore resorted to this same splitting of the gallbladder after removal of the stones, but supplemented it by trimming off the excess portion of the gallbladder close to the fossa in the liver, attempting to obtain the effect of a complete cholecystectomy, to permit drainage of the cystic duct and to avoid a two-stage operation, as is often necessary when only cholecystostomy is done. This partial cholecystectomy I have used in seven carefully selected cases. Convalescence has usually been uneventful; there have been no mortality and no evidence of peritonitis.

OPERATIVE PROCEDURE

The gallbladder is exposed by an incision through the upper part of the rectus muscle. It is carefully surrounded by gauze packs, and the bile and fluid contents of the gallbladder are removed by aspiration. The fundus is then incised, and stones, if present, are removed. The gallbladder is dried and swabbed out with tincture of iodine. It is split from the fundus down to the cystic duct, and partially removed by trimming away the redundant part of each half down to the border of the liver. The bleeding from this cut edge is controlled by ligature or lock stitch up each side. Two or more cigaret drains are placed close about the cystic duct and brought out against the remnant of the gallbladder; the omentum is carefully tucked in between these drains and the duodenum, and the wound is closed.

REPORT OF CASES

Brief abstracts of seven cases are appended to show, particularly, the end-results.

CASE 1.—History.—A man, single, aged 40, for six years had had a dull pain in the upper right quadrant of the abdomen, one-half hour after meals, which was relieved by soda. This pain recurred every month. There was no jaundice. Nineteen years before admission to the hospital, the patient had had a triple amputation, in which both thighs and the left arm had been removed.

Examination.—The patient had a round, thick, obese torso. There was no jaundice. The thighs had been amputated in the middle thirds, and good stumps had been left; the left arm had been amputated in the upper third. The abdomen was very fat, with slight tenderness over the right side of the hypochondrium. Roentgenograms showed a pathologic gallbladder. The results of the Fouchet test were positive.

Operation.—The abdominal wall was excessively thick and fat, the liver was high and enlarged, and the gallbladder was small, and thickened, with a tendency to obliterate and contained twelve stones. The common duct was normal on palpation. The gallbladder was exposed with great difficulty, and when removal was attempted, it ruptured near its base. The stones were removed, and a partial cholecystectomy was performed. The part of the gallbladder that was attached to the liver was allowed to remain, and three cigaret drains were inserted.

Course.—Vomiting continued until lavage on the second day. There was a brownish, serous discharge on the fifth day. The drains were removed on the eighth day. There was no biliary discharge. A small abscess (*Staphylococcus*

aureus) in the fat, lower angle of the wound appeared on the sixteenth day. The wound was completely healed, and the patient was discharged on the forty-second day.

Four years later, it was found that the patient occasionally belched gas. The wound was well healed, except for a postoperative hernia at the site of drainage. One month before the writing of this paper the patient was admitted to the medical service with jaundice and symptoms of obstruction in the common duct, which were relieved by Lyon biliary drainage. Twelve months later, there had been no recurrence of symptoms.

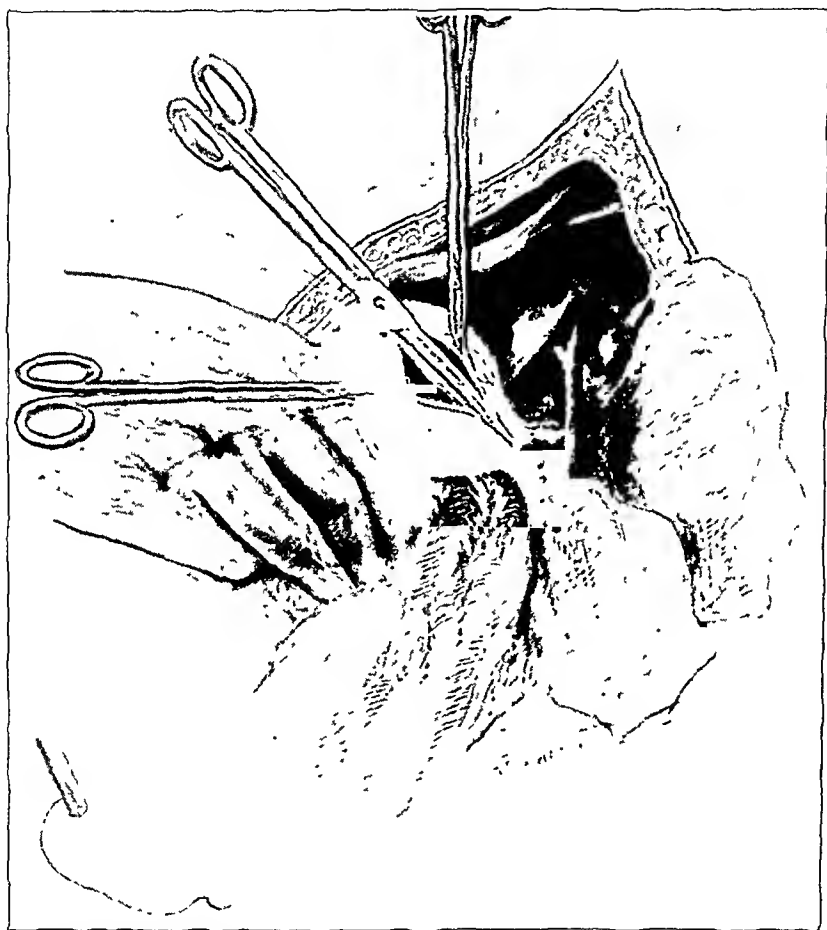


Fig. 1.—Splitting the gallbladder after aspiration (small inset), removal of the stones and swabbing with tincture of iodine.

CASE 2.—*History*.—A woman, aged 51, married, who had no children, underwent a bilateral oophorosalphingectomy at the age of 25. For seven weeks before admission to the hospital, she had frequent attacks of severe cramps in the upper right quadrant of the abdomen, radiating to the right shoulder and requiring morphia for relief. There was slight jaundice at the onset of the symptoms, with nausea and vomiting.

Examination.—The patient was obese and did not have jaundice. Marked tenderness, rigidity and an indefinite mass were present in the upper right quadrant of the abdomen. There was a well healed suprapubic scar. Examina-

tion of the blood revealed: white corpuscles, 17,200, and polymorphonuclears, 78 per cent. Urinalysis gave negative results.

Operation.—The patient was operated on one-half day after admission. The gallbladder was three times its normal size, gangrenous near its base and filled with stones (546) and thin, pale pus, not bile-stained. The gastrocolic omentum was adherent to it and was very thick and edematous. There were two large stones in the cystic duct, while examination of the common duct gave negative results. The gallbladder was isolated by packs, aspirated (the stones removed), swabbed with tincture of iodine and then split down through the ampulla. Partial cholecystectomy was done. Four cigaret drains were inserted. The culture from the gallbladder was sterile.

Course.—There was free biliary discharge for ten days, but the drains were removed on the seventh day. The patient was discharged on the twenty-first day, with the wound healed.

Four years later, the patient was found to be in excellent health, having had no indigestion, pain or discomfort since the operation.

CASE 3.—*History.*—A woman, aged 39, married, who had three children, had had pain in the epigastrium, radiating to the right shoulder and back by "spells" for three years. She had had the present attack for the last twelve days and intermittent cramps with vomiting, water brash and pain after the ingestion of food. Ten years before, she had had a complete hysterectomy.

Examination.—The patient was fat and not jaundiced. Marked tenderness, rigidity and an indefinite mass were present in the upper right quadrant of the abdomen. There was rigidity of the entire right rectus muscle, and a well healed suprapubic scar. Examination of the blood revealed: white corpuscles, 6,400; polymorphonuclears, 82.5 per cent; hemoglobin, 80 per cent, and red corpuscles, 4,300,000. Roentgenograms showed a pathologic gallbladder. The Wassermann reaction was negative.

Operation.—The patient was operated on four days after admission. The gallbladder was thickened, inflamed and filled with thin fluid pus but no bile. Firm adhesions bound the omentum to the gallbladder, and one stone was impacted in the cystic duct. Examination of the common duct gave negative results. The gallbladder was carefully isolated by gauze packs, split from the fundus to the cystic duct, the redundant portion excised, and the stone removed. A lock stitch was used to control the oozing from the cut surfaces. Four cigaret drains were placed in the gallbladder fossa. The omentum was carefully placed against the under surface of the liver. Culture from the gallbladder showed *B. mucosus-capsulatus*.

Course.—The patient was febrile, with a temperature ranging from 100 to 102 F. for two days. There was biliary drainage on the fourth day. The drains were removed on the sixth day, and replaced by a tube. Purulent biliary discharge followed, and the tube was removed on the fifteenth day. The patient was discharged on the twenty-third day, with the wound practically healed, except for a superficial sinus with no drainage.

There was no recurrence of pain or indigestion for four years; it has not been possible to trace the patient for the last two years.

CASE 4.—*History.*—A woman, aged 45, married, who had four children, for five months had had attacks of severe epigastric pain radiating to both shoulders and back, with vomiting. These attacks occurred two or three times a month. The last attack was on the day before admission.

Examination.—The patient was stout, with a faint icterus and marked tenderness in the upper right quadrant of the abdomen. Examination of the blood revealed: white corpuscles, 15,000; polymorphonuclears, 79 per cent, and an icterus index of 13. The roentgenogram showed gallstones and a poorly filling gallbladder.

Operation.—The patient was operated on three days after admission. The liver was cirrhotic with a huge gallbladder, the walls of which were 1 cm. thick. One large stone was impacted in the cystic duct. A hard, indurated omentum was



Fig. 2.—Suturing the cut margins of the gallbladder with lock stitch at the edge of the gallbladder fossa, the remainder of the gallbladder having been removed.

adherent to the gallbladder. Examination of the common duct gave negative results. The gallbladder was isolated, aspirated, incised and swabbed thoroughly with tincture of iodine. The stone in the cystic duct could not be removed until the gallbladder was split down to the cystic duct. The free portion of the gallbladder was cut away, and the cut edge sutured with a lock stitch. Four cigaret drains were used to hold the gallbladder fossa open and to drain the cystic duct, and the omentum was placed against them. A culture from the gallbladder was sterile.

Course.—The patient had a slight fever for four days, with only a serous bile-stained discharge. The drains were removed on the sixth day. She was discharged on the thirteenth day, with a slight, persistent sinus.

Two years later, the patient was completely relieved from symptoms, the wound had healed well, and there was no hernia. She had had no pain in the upper quadrant of the abdomen or indigestion since the operation. Recently, she had had a pain in the lower part of the right side suggesting appendicitis.

CASE 5.—History.—A woman, aged 45, married, who had no children, had had a hysterectomy for fibroids ten years before admission to the hospital. She had never been pregnant. She had had attacks similar to her present illness one and two years before, but these had been mild and of brief duration. Twenty-four hours before admission to the hospital, while she was washing clothes, she was seized by a sudden, severe pain, with vomiting, which steadily persisted, and which was relieved by morphine two hours before admission.

Examination.—The patient was moderately obese and slightly jaundiced; her teeth were in bad condition, and there were marked rigidity and tenderness in the upper right quadrant of the abdomen. No mass could be palpated, and there was a well healed suprapubic scar.

Examination of the blood revealed: white corpuscles, 26,650; polymorphonuclears, 94 per cent, and ieterus index, 8. Urinalysis showed a trace of albumin, sugar and bile.

Operation.—The patient was operated on on the day after admission. There was an excess of turbid, peritoneal fluid. The gallbladder was very large and completely detached from the liver, except at the ampulla and cystic duct. There was no gallbladder mesentery. The gallbladder was thick and acutely inflamed, containing many large and small stones, with one impacted in the cystic duct. The common duct was edematous, but there was no stone. The pancreas was thickened. The gallbladder was isolated and aspirated, the stones were evacuated, and the entire cavity was swabbed with tincture of iodine. It was then resected, except for a small portion adherent to the liver above the cystic duct for 2 cm. This, and the cystic duct were split wide open, the excess margins trimmed away, and the cut surface sutured by lock stitch. Tincture of iodine was applied to the remnant that remained, and three cigaret drains were placed in and about the cystic duct. *Streptococcus* was cultivated from the bile of the gallbladder.

Course.—There was little if any drainage, with slight fever for five days and very light nausea. The drains were removed on the sixth day. The patient was discharged on the eleventh day, with a small discharging sinus.

Three months later the wound had healed well. There was a slight keloid. The patient was able to eat liberally without indigestion.

One year later, the patient was entirely well, with no recurrent pain or indigestion.

CASE 6.—History.—A man, aged 73, married, had had upper abdominal pain for many years, steadily increasing jaundice for two months, with slight variable abdominal pain, anorexia and normal stools.

Examination.—The skin was bronzed, and there was an icteric tint to the sclerae. The teeth were abscessed and there was upper dorsal kyphosis. Emphysema was also present. The liver was large with an irregular edge, and there was tenderness but no definite mass in the region of the gallbladder. Roentgenograms showed the duodenum to be deformed from pressure from without. The icterus index was 13.5. Examination of the blood revealed: white corpuscles, 12,850;

polymorphonuclears, 70 per cent; red corpuscles, 3,930,000, and hemoglobin, 80 per cent. There was a trace of albumin and hyaline casts in the urine.

Operation.—The patient was operated on three days after admission. There was marked cirrhosis of the liver. The gallbladder was hugely distended and almost gangrenous, containing 120 cc. of thin, pale green fluid and numerous small stones. The hepatic flexure was adherent to the fundus. There was induration of the cystic and common ducts. The entire pancreas was thickened. The adhesions were separated, and the gallbladder was isolated, aspirated, incised widely and swabbed with tincture of iodine, and the stones were removed. Two

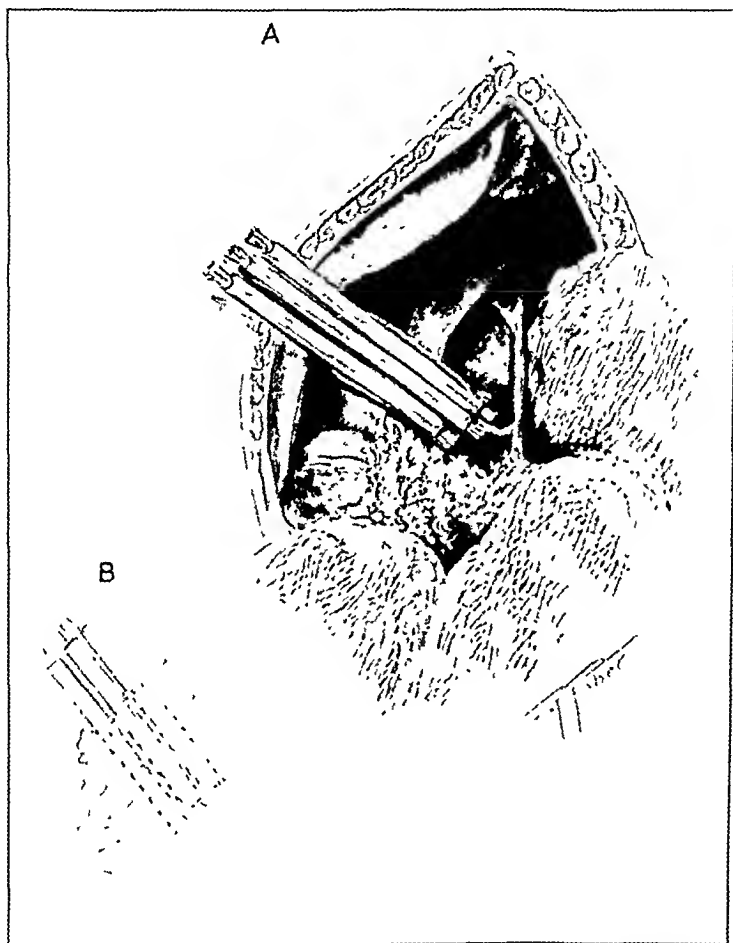


Fig. 3.—*A*, drainage of the area of the gallbladder with cigaret drains. *B*, the omentum tucked between the drains and the nearby viscera.

stones were also taken from the cystic duct. Partial cholecystectomy was performed, but no opening into the common duct was found. One tube was placed in the cystic duct, and four cigaret drains were inserted. A culture from the gallbladder was negative.

Course.—There was no drainage from the cystic duct, but on the fourth day, the jaundice was much decreased. The drains were taken out on the sixth day. The patient was discharged on the twenty-first day, free from jaundice, with the wound well healed.

Six months later, the patient was completely relieved and well.

CASE 7.—History.—A woman, aged 73, married, had had previous attacks twelve years and one week before admission. Two days before, severe pain developed in the upper right quadrant of the abdomen, which radiated to the shoulder and which persisted fairly constantly. Morphine¹ was given for relief. There was slight jaundice.

Examination.—There were tenderness, rigidity and a mass in the upper right quadrant of the abdomen. Urinalysis gave negative results. Examination of the blood revealed: white corpuscles, 16,900; polymorphonuclears, 80 per cent, and blood urea, 23.

Operation.—The patient was operated on four days after admission. Spinal anesthesia was used. The gallbladder was completely gangrenous, moderately enlarged and surrounded by thick, plastic omental adhesions, partially perforated near the fundus. It contained thick, pale pus and three large, and numerous small, stones. One large stone was impacted in the cystic duct. The common duct and pancreas were normal. A culture from the gallbladder grew *Bacillus coli*. The gallbladder was aspirated and split wide open, and the stones were removed. Partial cholecystectomy was performed, and one tube was placed in the stump of the cystic duct. Four cigaret drains were also inserted.

Course.—There was free biliary drainage on the fifth day, and all drains were removed on the ninth day. The patient had no fever, and was discharged on the eighteenth day with a wound completely healed, except for a small sinus.

Three months later the wound was well healed and there had been no hernia. The patient was well and free from pain and indigestion.

Comment.—It will be observed that partial cholecystectomy has been used six times in cases of acute cholecystitis with a stone impacted in the cystic duct, and once in the case of a hugely fat man with a thick, round torso, in which the operation was exceedingly difficult and complete cholecystectomy seemed impossible.

The patients with impacted stone in the cystic duct have shown no evidence of recurrence. Two have been followed for four years. The patient in case 1 recently had symptoms of involvement of the common duct.

Tincture of iodine was used to sterilize and destroy the mucosa of the remnant of the gallbladder. The actual cautery, however, may be more effectual, as Pribram¹ recently suggested.

COMMENT

Partial cholecystectomy, I find, is not a new procedure. In 1899 and again in 1900, W. J. Mayo² reported cases, particularly of obstruction of the cystic duct, in which removal of the stones and the mucous membrane of the gallbladder was done instead of complete cholecystectomy. Partial cholecystectomy was described in 1920 by Ben-

1. Pribram, B. O.: *Zentralbl. f. Chir.* 55:773, 1928.

2. Mayo, W. J., in Mayo, W. J., and Mayo, C. H.: *Collection of Papers Previous to 1909*, vol. 1, pp. 348 and 355.

golea.³ In 1921, E. D. Martin⁴ cited five cases of acute cholecystitis in which he had removed the stones, split the gallbladder and held it wide open with drains.

In 1923, De Martel,⁵ in a series of fifty-two operations on the gallbladder reported that in two, in which it was difficult to separate the ampulla and the cystic duct from adjacent structures, he split the gallbladder from fundus to ampulla, divided the cystic duct and cut away the free part of the gallbladder, swabbed the remaining portion with tincture of iodine and drained it. Both patients recovered.

In 1924, Zabala and Bengolea⁶ cited four cases of partial cholecystectomy with recovery; in one there was a mass of adhesions about the gallbladder; in another a calculus was impacted in the cystic duct, which was firmly indurated and adherent to the common duct; and in a third, a piece of the gallbladder was left near the cystic duct because of the friability of the tissue. They expressed the belief that the operation is indicated in severe suppurative cases in which resection would be fatal. The gallbladder is split and the stones are removed. Then the gallbladder is resected, leaving a portion attached to the liver; the mucosa of this remnant is curetted, and tincture of iodine is applied.

Pauchet⁷ decided that partial cholecystectomy was indicated: (1) in feeble or icteric patients, with stones in the common duct and gallbladder; (2) in atrophic gallbladder with stones; (3) in cases of subacute or acutely inflamed gallbladder adherent to the adjacent organs, and in (4) suppurating cholecystitis with fever. He believed that this operation avoids cholecystectomy when cholecystectomy would give a mortality of 50 per cent. He followed Zabala and Bengolea's technic, except that the remaining mucosa is swabbed with ether as well as with tincture of iodine, and when there are strong adhesions to the nearby intestines, the gallbladder is freed from the liver, and the portion adherent to the intestine is allowed to remain. The operation has been performed only in carefully selected cases in which cholecystectomy seemed to be indicated, but would be a dangerous procedure because of technical difficulties or the amount of infection present. In 1927, Gatch⁸ and Zimmerman⁹ referred to similar procedures before the Western Surgical Association.

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CONCLUSION

Partial cholecystectomy has, and should have, a restricted field. In patients in whom the surgical risk is thought to be great it should not replace cholecystostomy. Evidence of recurrent disease in the biliary tract has appeared in but one of seven cases, and in none of the cases in which a stone was impacted in the cystic duct. If argument were justified, based on so few cases, it would seem that this operation tends to act as a cholecystectomy—it prevents reformation or regeneration of the gallbladder and yet permits drainage as in cholecystostomy. It might, therefore, also have a field of usefulness in the rare type of secondary operation on the gallbladder in which, owing to adhesions or to a liver that cannot be rotated, cholecystectomy, although indicated, would be impossible.

SUMMARY

1. Partial cholecystectomy in properly selected cases seems a safe procedure.
2. Its chief indication is in acute cholecystitis when a cholecystectomy is indicated and is technically impossible or unsafe, particularly in cases of an impacted stone in the cystic duct.
3. It should never be used when cholecystectomy can be safely performed.
4. The end-results in seven cases are reported.

SPONTANEOUS RUPTURE OF THE URINARY BLADDER

REPORT OF TWO CASES *

ERIC STONE, M.D.

PROVIDENCE, R. I.

Rupture of the bladder by penetrating wounds was familiar to the ancients. Homer describes the death of Phereclus due to a spear wound passing from the buttock, through the perineum into the bladder. Spontaneous rupture, however, seems to have been recognized rather late in the history of medicine, as the first recorded case that an extensive review of the literature reveals is that of Pierus in 1279. For the next five centuries the cases of rupture of the bladder that were found were all of the traumatic type. The next reported case of spontaneous rupture was presented by Johnstone in 1773. Reports have become increasingly frequent since that time, until it is possible to review forty such cases to date. To these are added the two cases reported in this article.

The paucity of cases may seem surprising, but it is partially due to the definition of the term "spontaneous rupture." The various interpretations of its meaning by different authors has led to considerable ambiguity in the classification of cases. Some authors, for example, have reported as "traumatic" cases in which a fall or a blow caused the rupture of the distended viscus without any penetrating wound of the bladder, while other writers have considered similar cases spontaneous. For this type of case, the term "concussional" is proposed. Again, fistulas between the bladder and the intestinal tract due to inflammatory adhesions between the two structures with destruction of tissue at the point of contact have been considered under the heading of rupture of the bladder by some authorities and as essentially enterologic lesions by others. They should be placed in the same category as vesicovaginal and vesico-uterine fistulas, and not be classified under ruptures.

A clearer classification will be achieved if the term "rupture" is used to connote an evacuation of the bladder contents into a closed cavity, of which only two are accessible, namely, the perivesical space and the abdominal cavity. The term spontaneous rupture should be applied to those cases resulting from pathologic changes in the wall of the bladder or obstructive lesions at the neck of the bladder or in the urethra,

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* From the Gynecological Service of the Rhode Island Hospital.

irrespective of the presence or absence of pathologic changes in the bladder. With this redefinition in mind, the following classification is proposed for cases of rupture of the bladder:

I. Traumatic

A. Penetrating Wounds

1. By objects entering from outside the body
2. By objects entering from inside the body as
 - (a) Bone fragments
 - (b) Foreign bodies harbored within the body

B. Concussional (Falls or Blows Not Causing Penetrating Wounds of the Bladder)

II. Spontaneous

A. Inflammatory Lesions of the Wall of the Bladder

1. Intramural origin
2. Extramural origin

B. Malignant Disease of the Wall of the Bladder

1. Intervesical
2. Intravesical
3. Extravesical

C. Obstructive Changes at the Neck of the Bladder

1. Prostatic enlargement
 - (a) Benign
 - (b) Malignant
 - (c) Inflammatory (including seminal vesiculitis)
2. Calculi
3. Paralytic
4. Uterine and adnexal disease in the female
5. Occurring during labor

D. Obstructive Lesions in the Urethra

1. Strictures
2. Valves diverticula
3. Tumors
4. Calculi
5. Peri-urethral inflammation
6. Peri-urethral tumors

REPORT OF CASES

CASE 1.—R. S., a girl, aged 9½ years, was admitted to the orthopedic service on Nov. 22, 1928, complaining of a limp. The father and mother were living and well; there were six siblings living and well; none was dead. There was no tuberculosis in the family. The child had been admitted to the hospital on Sept. 21, 1922, with an infected right foot. She was discharged in ten days, against advice, with the foot and lower part of the leg swollen and reddened and a temperature of 100 F. She was readmitted on May 18, 1924, with osteomyelitis (nontuberculous) of the right os calcis, right hip and right ulna. She was again admitted on Sept. 11, 1924, with abscess in the right heel from osteomyelitis of the os calcis. On July 2, 1926, she came to the hospital for operative correction of the deformity of the right hip. She had been well until one week before the last admission, when she began to limp, developed pain in the right hip and fever.

Examination.—On physical examination, areas of dulness were found on percussion at the apex of both lungs, with moist râles on both sides throughout. The fremitus was normal. The edges of the kidney, liver and spleen were not palpable. There was tenderness in the right lower quadrant extending down into the right groin and most marked over the hip joint. No masses, spasm or rigidity were noted. Motions of the hip were limited in all directions and were painful. Roentgen examination on Nov. 23, 1928, showed no evidence of pathologic process in the dorsal or lumbar spine. There was considerable increased density in the lung markings. The changes noted in the chest could be due to tuberculosis. On the day of admission, the urine was clear, yellow, acid, with a specific gravity of 1.026 and no albumin or sugar; the sediment showed a rare leukocyte. On November 23, the leukocyte count was 15,000, with 83 per cent polymorphonuclears. The vaginal smear was negative.

On December 7, frequency, burning, spasm and extreme dysuria suddenly developed. The urine passed was thick with pus. The child had never before had any urinary symptoms. Urinalysis showed thick yellow urine with a specific gravity of 1.024, acid, no sugar, a large trace of albumin and sediment loaded with pus. No tubercle bacilli were seen.

Operation and Course.—On December 12, an incision was made, and the abscess in the right hip was drained. There was a fluctuant area over the old scar. A considerable quantity of watery, blood-colored fluid flowed from the wound. A cigaret drain was inserted, and a catheter was introduced into the bladder, but no urine was obtained. On pressing the lower part of the abdomen, a mucopurulent fluid was expressed from the vagina. Rectal examination gave negative results, no areas of fluctuation or induration being noted (Dr. Murray Danforth). On December 12, a culture of the pus from the hip showed gram-positive cocci, *Staphylococcus aureus*. No tubercle bacilli were found in the smears. The child had voided nothing by the urethra since operation, but on December 22, the dressing on the wound in the right hip was saturated with urine. Cystoscopy (Dr. Stone) was done with the child under gas-oxygen anesthesia. A no. 18 F. cystoscope entered the bladder easily. Thick pus was obtained. The fundal mucous membrane was everywhere intensely red and swollen. No stones, ulcers, tumors, diverticula or trabeculae were seen. The trigone, which could not be defined as to its limits, as well as the sphincter partook of the generalized inflammatory reaction. The right orifice was vulvalike and about 1 cm. in length. It admitted a no. 5 x-ray catheter, which passed freely to the pelvis. The left orifice was normal and admitted a catheter to the pelvis. About 2 cm. directly posterior to the right orifice was a circular opening in the wall of the bladder which looked like the mouth of a diverticulum; a catheter was passed into this up to 10 cm., giving the impression that it coiled up out of sight as it was fed into the orifice.

The urine from the kidneys was slightly blood stained, and the flow was rapid and regular. Culture of the urine from both kidneys was sterile. A smear of the urine from the right kidney showed few white blood cells, few epithelial cells and a moderate number of red blood cells; that from the left kidney showed few red blood cells, few white blood cells and epithelial cells. Phenolphthalein, injected intravenously, appeared in the urine from the right kidney in eight minutes and in that from the left kidney in twelve minutes. In fifteen minutes, the urine from the right kidney showed 2.5 per cent phenolphthalein and that from the left kidney 4 per cent. The stain for tuberculosis was negative; the guinea-pig test

was also negative. The capacity of the pelvis of the right kidney was not obtained, but into the left kidney 5 cc. of 12.5 per cent solution of potassium iodide was injected.

Twenty-five cubic centimeters of potassium iodide was injected through the catheter, introduced into the rent in the wall of the bladder. The pelvis of the left kidney and the calices were well outlined after injection. There were many dense, irregular shadows at the level of the third and fourth lumbar vertebrae, probably due to calcified glands. There was an opaque catheter in each ureter. There was also a third catheter projecting to the right of the median line with



Fig. 1 (case 1).—Catheter in position; *A*, catheter in the right ureter; *B*, in the left ureter and *C*, in the perivesical tissue.

several loops, apparently outside the wall of the bladder. The loops were probably in the tissues outside the ruptured area. The opaque solution had been injected through this catheter and could be seen near the pelvic brim and also overlying the wing of the right ilium (Dr. James Boyd) (figs. 1 and 2).

On Jan. 7, 1929, after the injection of sodium iodide into the bladder, a cystogram of the region of the bladder and right hip showed evidence of the opaque material extending from the bladder laterally, then downward anterior to the acetabulum, then downward and posterior to the femur to the lateral aspect of the thigh (Dr. Philip Batchelder) (fig. 3). Although the patient had voided

nothing by the urethra from December 7 to 23, she urinated within six hours of the cystoscopic examination and has continued to do so. Micturition was associated with considerable dysuria for about two weeks. The urine was loaded with pus cells for about three weeks. Microscopic examination of the sediment after centrifugation showed a few leukocytes on February 15, and only a rare leukocyte on April 10. The sinus at the right hip became permanently closed on January 31. Medicinal measures alone were used, compound methylene blue (methylthionine chloride, U.S.P.) being the only urinary antiseptic presented. Conva-



Fig. 2 (case 1).—After the injection of potassium iodide solution into the left kidney pelvis and sinus. *A* shows the catheter in the right ureter; *B*, the pyelogram of the pelvis of the left kidney; *C*, potassium iodide solution in the bladder; *D*, in the perivesical space; *E*, passing anterior to the anterior superior spine; *F*, around the acetabulum and head of the right femur.

cence was complicated by an acute inflammation of the middle ear on January 23, which soon subsided. The temperature remained normal after February 21, and on April 12, the patient was discharged to the Crawford Allen Memorial Convalescent Home.

CASE 2.—*History*.—R. W., a man, aged 67, was admitted to the Rhode Island Hospital on Nov. 25, 1891, dangerously ill, complaining of pain in the left lower quadrant of six days' duration. He had had frequency and nocturia for some years and for one year had been troubled by "gravel" passing by the urethra. Since the onset of the present illness, he had passed only a few drops of thick, bloody urine. The temperature was 104 F. on admission, and the patient was toxic and difficult to arouse.

Examination.—Physical examination showed as noteworthy features marked tenderness and spasm and some induration in the left lower quadrant. There

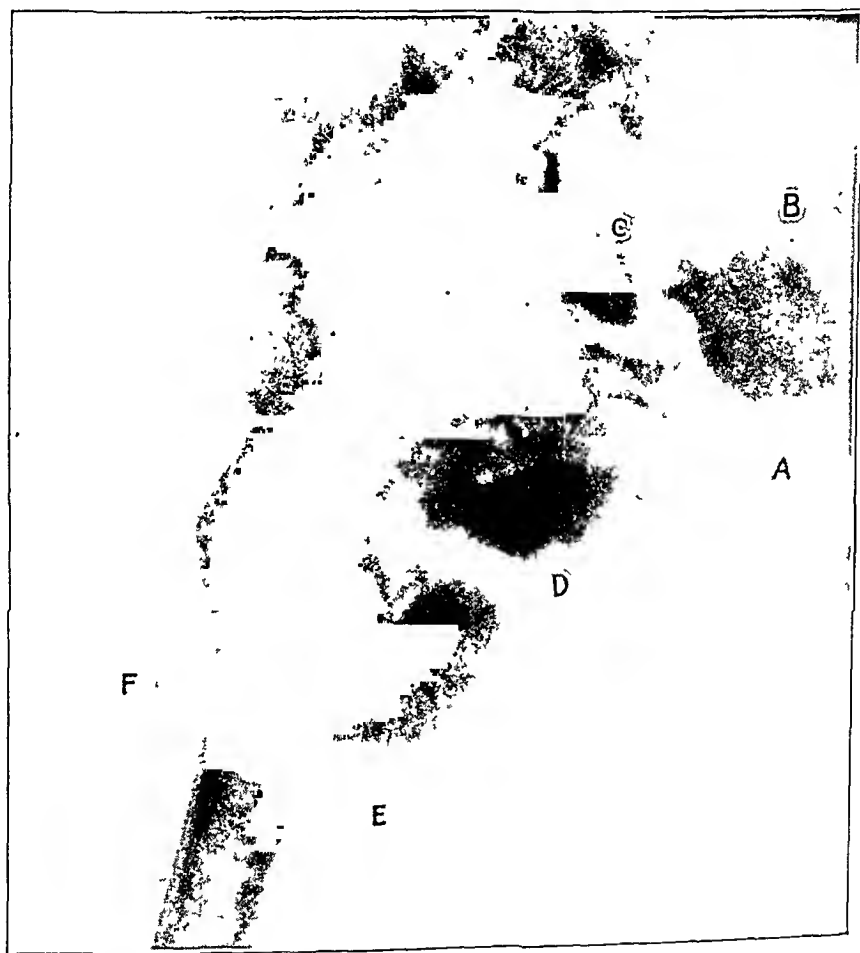


Fig. 3 (case 1).—Cystogram. *A* shows the catheter in the ureter; *B*, the potassium iodide solution in the bladder; *C*, in the perivesical space; *D*, potassium iodide solution near the acetabulum; *E*, back of the great trochanter and passing posteriorly to a subcuticular position, *F*.

was a right inguinal hernia, which had been present for twelve years. A catheter was passed into the bladder with ease, but only a few drops of blood-stained purulent fluid was obtained. Boric solution, 550 cc., was introduced through the catheter, but only 30 cc. was recovered. By sound, an endeavor was made to find a possible vesical calculus but none was demonstrated.

Operation and Course.—Operation was performed on November 27 by Dr. Mitchell. A suprapubic midline incision was made and the peritoneum opened,

but no fluid was found in the abdominal cavity. The peritoneum was repaired, and the incision carried down over the bladder, which was opened in the midline. No stones or urine were found, and no rupture was located. There was extensive extravasation of urine throughout the left side of the space of Retzius, and amid much necrotic and purulent matter a vesical calculus the size of a bean was found. The bladder was closed around a drainage tube, and a drain was placed in the area of extravasation. The wound was then closed in layers about the two drains. The patient left the operating room in a state of shock. He did not rally from the operation; no urine was discharged while in the hospital, and he died on November 29.

Case 1 has four points of interest: 1. It demonstrates the distance from which inflammatory lesions may burrow to reach the wall of the bladder and then cause enough inflammatory reaction to result in rupture. 2. What part the trigone and sphincter played in producing the rupture is not clear. Obviously there was a profound disturbance of the sphincteric function if the failure to void was due to the pathologic process at this point. There are two possibilities. The early frequency and dysuria may have expressed an irritation from perivesical inflammation, which, as it progressed, rendered the trigonal muscle incapable of action, and the subsequent retention precipitated the rupture, or the rupture may have occurred early, and the free drainage of urine through the rent made voiding unnecessary. 3. It is also obvious that some factor involved in the cystoscopic examination so altered conditions that the patient voided within six hours of the procedure, although for the ten preceding days she had passed nothing through the urethra. The factors involved were mechanical dilatation of the neck of the bladder, prolonged and thorough irrigation of the bladder and sinus tract with boric solution and injection of 12.5 per cent potassium iodide solution into the site of the rupture. 4. The fourth point of interest is spontaneous cure in a case of spontaneous rupture of the bladder. The second case reported here is interesting more as a curiosity than for its scientific value. It occurred before the modern era of careful study and case recording, and the hospital record was far from complete. Apparently a vesical calculus caused sufficient inflammatory reaction in the wall of the bladder to penetrate it and emerge in the perivesical tissues. Two other possibilities present themselves. The calculus may have become impacted in the neck of the bladder and caused a rupture by obstruction and later may have fallen out of the bladder through the rent, although in such a case one would have expected the rent to be posteriorly at the vault, which would have caused an intraperitoneal rupture; or there may have been a rupture of the ureter proximal to the physiologic intramural constriction, as no rent in the bladder was discovered. But in such a case the greatest changes would have been expected at the base, rather than laterally and anteriorly.

INCIDENCE

At the Rhode Island Hospital, 1868-1929, 2 cases of spontaneous rupture were found in 226,632 total medical and surgical admissions. Quick reported the incidence of all types of ruptures of the bladder as follows: Cook County Hospital, 1889-1893, 5 cases of all types in 8,000 surgical admissions; St. Bartholomew's Hospital, 1869-1875, 2 traumatic cases in 16,711 admissions, and Episcopal Hospital, Philadelphia, 1900-1905, 3 intraperitoneal cases in 8,367 admissions.

PATHOLOGY

In all cases either one of two conditions was present at the time of the rupture; in only a few were both present simultaneously. There was either chronic or temporary obstruction to the urinary outflow, or there was a destructive lesion of the wall of the bladder. There were twenty-one cases of obstruction, and only twelve of lesions of the bladder, while in nine the description was not sufficient to determine the type (table 1). In eighteen of the cases, no abnormality of the wall of the bladder was discovered at the site of the rupture. In thirty of the cases of intraperitoneal rupture, the site is recorded. In twelve cases, rupture occurred at the vault in the midline or just below it, which is as would be expected in that developmentally this is one of the weak points in the musculature of the bladder, and structurally it is the part furthest removed from the support of surrounding tissues. In the only case reported in which rupture occurred near the base of the bladder, an old scar from a retroperitoneal hematoma was found at the site. Again, as would be expected, the preponderance of intraperitoneal ruptures resulted from an obstructive pathologic process (fifteen intraperitoneal to six extraperitoneal); whereas the preponderance of extraperitoneal ruptures occurred in the same ratio, in cases in which there was a pathologic process of the vesical wall.

There were two cases of extraperitoneal rupture dependent on obstructive pathologic process which are interesting because of the site of the ruptures. One was just medial and posterior to the right ureteric orifice, while the other bore the same relation to the left orifice. These two points are apparently inherently weak, despite surrounding structures, as they are the most frequent site of diverticulae, especially of the congenital type.

As to the pathologic process in the wall of the bladder in the ten cases in which such a process was found, the predominant lesion was ulceration of the wall. In the cases in which the lesions were obstructive in twenty-four the descriptions were clear, urethral stricture occurred nine times, dry labor five and prostatic hypertrophy three times (table 1).

ETIOLOGY

The precipitating cause, over and above the situation created by the pathologic process present, in twenty-one cases in which a description was given in the case reports, was invariably a sudden increase in intra-abdominal pressure. The specific causes are as follows: manual expression of the placenta five days post partum, 1; rupture of distended bladder during labor, 5; attempted micturition during acute retention, 6; intoxication (no history or evidence of any type of trauma), 3; straining at the stool, 3; sudden lifting of a weight, 3.

MORTALITY

The mortality in rupture of the bladder before 1900 was appalling. The elder Lally, in 1817, was the first person to maintain that a patient

TABLE 1.—*Pathology and Site*

Pathology	Number	Site	Number
Bladder		Intraperitoneal type.....	30
No lesion found.....	21	Top of vault in midline.....	6
Ulcer.....	4	Just below top in midline....	6
Cancer.....	2	Posterior inferior fundus....	2
Diverticulum.....	1	Right side near vault.....	1
Trabeculum.....	1	Left side near vault.....	1
Old scar.....	1	Extraperitoneal type.....	12
Calculus.....	1	Middle of trigone.....	1
Prostatic hypertrophy.....	3	Anterior wall of fundus.....	1
Urethra		Right near ureteric orifice...	1
Stricture.....	9	Left near ureteric orifice....	1
Calculus.....	2	Site in obstructive lesion	
Impervious.....	1	Extraperitoneal.....	6
Perivesical cellulitis.....	2	Intraperitoneal.....	15
Retroversion of uterus.....	1	Site in lesions of bladder wall	
Dry labor.....	5	Extraperitoneal.....	15
Paralysis.....	1	Intraperitoneal.....	6

might recover from such an accident. S. S. Smith recorded seventy cases of all types up to 1851, with a mortality of 93.5 per cent. By 1893, A. R. Quick was able to show improvement as far as traumatic intraperitoneal rupture was concerned, presenting a mortality of 24.1 per cent. Since 1900, there has been a marked diminution of fatalities.

If only the cases of spontaneous rupture are considered (table 2), the ratio of improvement is much the same. Full descriptions of the treatment and of the end-results were available in only twenty-seven cases. The mortality in all cases of spontaneous rupture up to 1900 was 78.9 per cent, while that from 1900 to the present fell to 27.2 per cent. The rates for intraperitoneal spontaneous ruptures are uniformly higher than those in which the rent opened extraperitoneally. Among the former, the mortality rate was 92.3 per cent prior to 1900 and 45.4 per cent subsequently. The latter figure is reduced to 33.3 per cent if the two cases are excluded in which death occurred so promptly that treatment could not be instituted.

The extraperitoneal type of spontaneous rupture seems to be the least fatal. Even in the period up to 1900, the mortality rate was only 50 per cent as compared with 92.3 per cent for intraperitoneal rupture. In the last thirty years, there are no recorded fatalities in perivesicular extravasation, in sharp contrast to a mortality rate of 45.4 per cent for the intraperitoneal type.

DIAGNOSIS

The clinical pictures varied widely, depending to a great extent on the basic pathologic process. Furthermore, the site of the extravasation alters the symptoms, contingent on its extraperitoneal or intraperitoneal position.

TABLE 2.—*Mortality in Spontaneous Rupture**

Type	1279-1899		1900-1929	
	Treatment	Cured Dead	Treatment	Cured Dead
Intra-peri- toneal	None.....	.. 1	None.....	.. 2
	Laparotomy, rent repaired, no bladder drainage.....	.. 1	Laparotomy, rent repaired, no bladder drainage.....	5 2
	Laparotomy, rent repaired, urethral drainage.....	1 1	Cystotomy only, rent re- paired, urethral drainage...	1 1
	Medicinal.....	.. 7		
	Bladder drained by rectal puncture.....	.. 1		
	Totals.....	1 12	Totals.....	6 5
	Mortality, 92.3%		Mortality, 45.4%	
Extra- peri- toneal	None.....	.. 1	None.....	1 ..
	Perineal section.....	.. 1	Cystotomy, perivesical, drainage rent unrepaired...	2 ..
	Perineal section, bladder drainage through rent.....	1 ..	Same, but rent repaired.....	2 ..
	Catheter drainage only.....	1 ..	Cystotomy only.....	1 ..
	Cystotomy, perivesical drain- age.....	1 1	Perineal section, drained through the rent.....	1 ..
	Totals.....	3 3	Totals.....	7 0
	Mortality, 50%		Mortality, 0%	
	Totals.....	4 15	Totals.....	13 5
	Mortality, 78.9%		Mortality, 27.2%	

* Unless specified to the contrary "laparotomy" and "cystotomy" imply drainage.

In the intraperitoneal type, there is a history of chronic or more frequently acute retention with the sudden onset of severe lower abdominal pain during attempted micturition, defecation or other effort that may cause a sharp rise in intra-abdominal pressure. The history often contains the statement that at the time the patient "felt something give." The patients are often "in shock" when first seen by the physician, or seriously ill, and present the picture of an "acute abdominal condition." The intestines are distended and the abdominal wall is spastic and rigid from peritoneal irritation. Not infrequently shifting dulness may be demonstrated in the flanks.

The onset of the actual rupture in the extraperitoneal extravasation is usually insidious. The patients are not seen by the consultant at the hospital until several days have intervened. At this time they present

the picture of sepsis. There is tenderness and edema above the pubes, or it may be made out by vaginal examination in the female or rectal examination in the male around the base of the bladder or in the lateral aspects of the space of Retzius. Pedersen has called attention to a faint blush and tenderness about the umbilicus which may occur as early as the sixth hour after rupture.

The demonstration of the presence of a rupture was well conceived seven centuries ago and is still in use. The patient is catheterized. If a little blood-stained urine or if none is obtained, rupture is suspected. A measured amount of sterile solution is then injected through the catheter, and the amount of the return flow is noted. If only a little or none returns, it is assumed that the bladder is ruptured. Keen presented the next advance in diagnosis, which consisted of the injection of air instead of fluids in conjunction with the use of the x-rays. In more recent years, the cystoscope has been of definite diagnostic aid when extraperitoneal rupture is suspected. That the method is not harmful and may actually have some therapeutic effect, is demonstrated by the case reported here. When cystoscopy is contraindicated, as in extremely ill patients, or where intraperitoneal rupture is suspected, I should like to suggest the use of iodized poppy seed oil 40 per cent injected into the bladder, although I have not had the opportunity to use it in this connection. But some experience with its use in making hysterosalpingograms convinces me that the oil is not only nonirritating to the peritoneum, but is actually a mild antiseptic, as shown by improvement in cases of low grade chronic salpingitis after its use. The clearcut roentgenogram that it gives would certainly be a great aid to visualization of the existing conditions before operation is attempted.

TREATMENT

Within the last fifteen years, considerable advance has been made in the standardization of the operative technic for the treatment of rupture of the bladder. In all types, save the rare exception, the operative procedure is an emergency measure to be carried out as soon as the diagnosis is established.

The first operation for the relief of rupture of the bladder found recorded in the available literature was performed in a case in which paracentesis and insertion of an indwelling urethral catheter was done by Cusack in 1814. The patient died in eight days. Harrison did a paracentesis in 1836, and the patient died in forty-two hours. William Walker of Boston performed the first suprapubic cystotomy in a case of extraperitoneal traumatic rupture in 1845. Both the bladder and the space of Retzius were drained, and the patient recovered. In 1861, Walters of Pittsburgh operated in a similar case ten hours after the

accident. The space of Retzius was opened and drained. Urethral drainage of the bladder was established, but no attempt was made to sew the rent. The patient recovered. The first laparotomy with suture of the bladder hole was done by Willet in 1876; Heath reported a case in which similar treatment was done in 1879; Bull of New York, in 1885, and McGill of Leeds, in 1886, employed similar procedures, all with fatal results.

All these operations ignored the prime requisite for success, which is adequate drainage of the bladder. In the intraperitoneal type, the abdomen should be opened and efficient abdominal drainage provided. The abdominal cavity should not be flushed out, simply drained. There is no necessity for sewing the rent, provided the next essential step is taken; this is cystotomy, with the placing of a large suprapubic bladder drainage tube.

In the extraperitoneal type of rupture, the management of the bladder should invariably entail effective drainage, usually from above, rarely in basal ruptures, from below. There is less unanimity of opinion as to the care of perivesical cellulitis, except that free drainage must in some way be attained. In those cases of rupture near or in the trigone, Fuller advocated the perineal approach with drainage of the bladder through the rent and separate drains in the perivesical space. When the extravasations and inflammation are chiefly anterior or high in the lateral spaces, suprapubic cigaret drains of large caliber and suprapubic bladder drainage should be effective. When the position of the rupture or gravity has caused extensive reaction throughout or chiefly about the base, in addition to the inevitable suprapubic bladder drainage, the cigaret drains in the space of Retzius should be through and through, entering above, passing under the pubic arch and emerging from the perineum.

The opinion is becoming general that given free drainage of the bladder, the repair of the rent is unnecessary.

In the event of the survival of the patient, these emergency measures are merely precursors of such steps as will relieve the basic pathologic process.

SUMMARY

1. Spontaneous extraperitoneal rupture of the bladder is the least dangerous type of rupture.

2. Injection of iodized oil into the bladder is suggested as a diagnostic measure.

3. Under certain conditions, spontaneous cure may take place.

4. The two cardinal principles in the management of the emergency phase of such cases are: (a) adequate drainage of the bladder, and (b) adequate drainage of the space of Retzius.

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THE CAUSE OF DEATH IN ACUTE DIFFUSE PERITONITIS *

BERNHARD STEINBERG, M.D.

TOLEDO, OHIO

Of the several current conceptions regarding the cause of death in acute diffuse peritonitis, that of toxemia is the most commonly accepted. Until 1926,¹ no experimental evidence was offered to substantiate such a conception. Ecker and I² were able to produce the death of rabbits following the intraperitoneal injection of broth cultures of *B. coli*. The rabbits that received colon bacillus antiserum intravenously, in addition to the broth culture of colon bacillus intraperitoneally, survived. However, it was later demonstrated³ that introduction of broth cultures of colon bacillus into the peritoneal cavity of rabbits and dogs may result in the death of the animals, but not necessarily in peritonitis. Since the inflammatory peritoneal lesion was either absent or doubtful and the value of the colon bacillus antiserum is still questioned, the experiments of Ecker and myself are merely suggestive but are by no means conclusive of a bacterial toxin being responsible for death in peritonitis. The second experimental evidence was offered by Williams,⁴ who administered *B. welchii* antitoxin to patients with clinical evidences of a severe peritonitis. Williams obtained a large percentage of survivals in patients thus treated. He found a proliferation of *B. welchii* in the small intestine of patients with a low intestinal obstruction and a similar picture in the small bowel of dogs with an experimentally obstructed bowel. Williams hypothesized that death in intestinal obstruction and peritonitis was at least partly due to the absorption of *B. welchii* toxin from the stagnant small bowel. Again, the experiments are suggestive

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* From the Laboratories and Department for Medical Research, Toledo Hospital.

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1. Steinberg, B., and Ecker, E. E.: The Effect of Antiserum Against the Soluble Toxic Substance of Bacillus Coli in Bacillus Coli Peritonitis, *J. Exper. Med.* **43**:443 (April) 1926. Williams, B. W.: Peritonitis: The Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction, *Brit. J. Surg.* **14**:295 (Oct.) 1926.

2. Steinberg and Ecker (footnote 1, first reference).

3. Steinberg, B.: Drainage of the Thoracic Duct in Experimental Peritonitis, *J. Exper. Med.* **42**:83 (July) 1925.

4. Williams (footnote 1, second reference).

but are inconclusive. The patients might have recovered without treatment with *B. welchii* antitoxin. Furthermore, Williams' patients had peritonitis secondary to intestinal obstruction, and consequently, other factors may be present that are not found in primary peritonitis.

The nature of the toxic action is a matter of much speculation. The theory that a bacterial toxic substance paralyzes the medullary vascular centers has received an additional stimulus by the work of Manenkow.⁵ This investigator injected cultures of staphylococcus into the serosa of the stomach of rabbits with a resulting diffuse peritonitis and death of the animals. Similar amounts of a culture of staphylococcus introduced into the serosa of the colon resulted in a localized peritonitis and survival or prolongation of the life of the animals. Manenkow assumed that since the stomach has a direct nerve-lymphatic connection, death was due to the passage of the toxin along the lymphatics of the nerve with the subsequent action on the medullary centers. Kirschner⁶ pointed out that the fall in blood pressure in peritonitis occurs only a short time before death, and hence he doubts that the medullary vascular centers are affected by the toxins. Among other theories for which there is little or no evidence there is one which assumes that the toxin acts on the capillaries of the peritoneal cavity with injury and stagnation of the portal circulation.⁶ The conception that the intestinal paralysis is a deciding factor in the fatal outcome in diffuse peritonitis is receiving some consideration at present. Askanazy⁷ expressed the belief that the intestinal lymphatics dilate, press on the ganglion cells with a consequent paralysis of the intestines. Lennander⁸ agreed to the existence of intestinal paralysis and added that the passage of toxins and bacteria through the paralyzed bowel is responsible for death. As a result of a study of the chemical changes of the blood in intestinal obstruction and peritonitis, Orr and Haden⁹ stated that there has not been sufficient evidence to justify the belief that intestinal obstruction is alone the cause of death in peritonitis.

5. Manenkow, P.: Experimentelle Befunde zur Frage des Mechanismus einer direkten Affektion der Oblongata bei diffuser Peritonitis, *Ztschr. f. d. ges. exper. Med.* **64**:239, 1929.

6. Kirschner: Die Behandlung der eitrigen, freien Bauchfellentzündung, 50 Tag. d. deutsch. ges. f. Chir. Berlin, 1926; quoted in the *Internat. Abstract Surg.* **44**:276 (April) 1927.

7. Askanazy, quoted by Heineke, H.: Experimentelle Untersuchungen über die Todesursache bei Perforationsperitonitis, *Deutsches Arch. f. klin. Med.* **49**:429, 1900-1901.

8. Lennander, quoted in Kaufmann: *Lehrbuch der pathologischen Anatomie*, trans. by Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 2, p. 865.

9. Orr, T. G., and Haden, R. L.: Enterostomy in the Treatment of General Peritonitis, *Arch. Surg.* **18**:2159 (May) 1929.

It is necessary to differentiate between two conceptions regarding the origin of the toxin that is assumed to produce death. One group of workers¹⁰ believed that the toxic action is due to the toxins elaborated in the peritoneal cavity by the bacteria that had produced the peritoneal inflammatory lesion. The other group¹¹ is of the opinion that the fatal outcome is due to the toxins elaborated by bacteria within the bowel. With intestinal paralysis and stagnation, the toxins are absorbed or pass through the intestinal wall and into the circulation. However, no experimental evidence or sufficient clinical data has been brought forth to demonstrate that there is invariably an intestinal paralysis associated with a fatal outcome in diffuse peritonitis.

EXPERIMENTAL WORK

The following experiments were undertaken: (1) to ascertain the rôle of bacterial toxins in the outcome of diffuse peritonitis; (2) to determine the type of toxin (from the bacteria within the bowel or from bacteria within the peritoneal cavity) responsible for death; (3) to learn the effect of the toxins on the cellular reaction of the peripheral blood and that evoked in the peritoneal cavity. In order to accomplish these purposes, it was necessary to choose a micro-organism that is not found in the intestinal contents, that is a definite toxin producer and possesses a recognized antitoxin, and that is capable of producing invariably a fatal diffuse peritonitis in a laboratory animal. The diphtheria bacillus answered all these requirements.

In order to determine the effect of diphtheria toxin¹² on dogs, ten of these animals were given injections of varying amounts of toxin (from 0.5 to 2 cc.) intravenously, subcutaneously or intraperitoneally. The animals died in from eighteen to forty-eight hours after the injection of the toxin.

Production of experimental fatal peritonitis by known and controlled agents had met with difficulties in the hands of many investigators. The methods employed usually accomplished only a part of the required purpose. On the introduction of the agent, the animal died but had no peritoneal inflammation, or if a peritonitis was produced, the animal survived. Other methods that induced both the local peritoneal lesion and death produced these results only in a small and varying percentage of the experimental animals, and the methods employed contained unknown and uncontrollable agents. A procedure that fails to secure (in 10 per cent of animals) a definite peritonitis resulting in death lacks

10. Steinberg and Ecker (footnote 1, first reference). Manenkow (footnote 5). Kirschner (footnote 6).

11. Williams (footnote 1, second reference). Askanazy (footnote 8).

12. The diphtheria toxin was obtained from the laboratories of the New York State Department of Health through Miss Mary B. Kirkbride.

the essential requirements of a properly controlled experiment. A suggestion of a method that invariably results in a fatal peritonitis was made by Benians.¹³ He injected intraperitoneally into rabbits colon bacilli suspended in gum tragacanth. This procedure was later adopted for dogs and repeatedly confirmed.¹⁴

The principle of the method of Benians was adopted in these experiments. The saline washings of three blood agar slants of a twenty-four hour culture of diphtheria bacilli were suspended in a 2.5 per cent saline suspension of gum tragacanth and injected by means of needle and syringe through the abdominal wall into the peritoneal cavity of dogs.¹⁵ At the onset of the experiments, thirteen animals and later nine additional dogs, were given injections of this material. The twenty-two animals died in from eighteen to forty-eight hours of a severe fibrinopurulent hemorrhagic peritonitis.

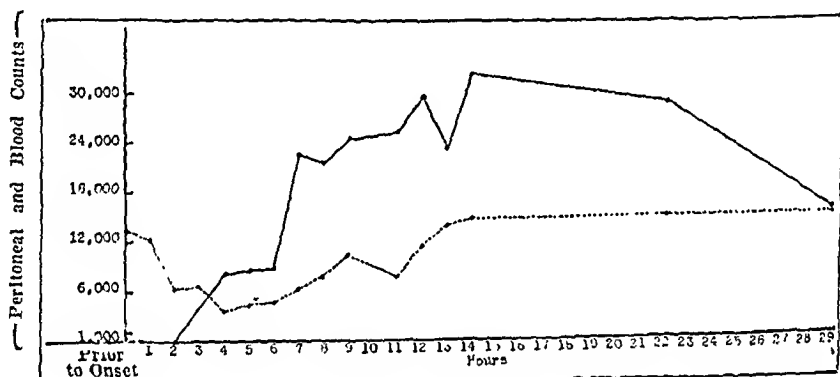


Chart 1.—Blood counts and peritoneal counts in a normal dog given injections intraperitoneally with three slants of diphtheria bacilli in gum tragacanth. The animal died. In this and the following charts the dotted line indicates the blood counts and the unbroken line the peritoneal counts.

It was assumed that if death of the twenty-two animals was due to the toxin liberated by the diphtheria bacilli, diphtheria antitoxin in sufficient amounts would neutralize the toxin and avoid death. To test this assumption, each of fifteen dogs were given injections intraperi-

13. Benians, T. H. C.: Further Experiments with Fixation Areas, Bearing on Pathogenicity of *Bacillus Coli* in Peritoneal Infections, *Brit. J. Exper. Path.* 5:123 (June) 1924.

14. Steinberg, B., and Goldblatt, H.: Studies on Peritonitis: II. Passage of Bacteria from the Peritoneal Cavity into Lymph and Blood, *Arch. Int. Med.* 39: 449 (March) 1927. Goldblatt, H., and Steinberg, B.: Peritonitis, Active Immunization Against Experimental *B. Coli* Peritonitis, *ibid.* 41:42 (Jan.) 1928. Steinberg (footnote 3).

15. It was found that a suspension of one slant injected into a dog weighing 10 Kg. invariably resulted in a fatal peritonitis.

toneally of the saline washings of three slants of a twenty-four hour culture of diphtheria bacilli suspended in 2.5 per cent gum tragacanth, and at the same time diphtheria antitoxin was administered by the routes indicated in table 1. (These fifteen dogs received the intraperitoneal injection at the same time as the first set of the thirteen control dogs.) All of the fifteen dogs that were given diphtheria antitoxin survived. The animals were slightly ill during the first eighteen hours but after that they were apparently well.

It was demonstrated previously¹⁶ that when bacteria (colon bacilli) are suspended in gum tragacanth and injected into the peritoneal cavity of dogs, the bacteria remain almost entirely in the peritoneal cavity. There is no passage of the micro-organisms into the circulation, and hence whatever struggle occurs between the defenses of the body and the invading bacteria takes place in the peritoneal cavity. Snyder and

TABLE 1.—*Effect of Diphtheria Antitoxin on Dogs in Which Peritonitis Has Been Produced by Diphtheria Bacilli*

No. of Dogs	Type of Material Injected Intraperitoneally	Units of Diphtheria Antitoxin Given	Route of Administration of Antitoxin	Outcome
13 9	Three slants of diphtheria bacilli in 40 cc. of a 2.5% suspension of gum tragacanth	None	Died in from 18 to 48 hours with a marked hemorrhagic peritonitis
11	Three slants of diphtheria bacilli in 40 cc. of a 2.5% suspension of gum tragacanth	20,000	Intravenously	Survived
2	Three slants of diphtheria bacilli in 40 cc. of a 2.5% suspension of gum tragacanth	20,000	Intramuscularly	Survived
1	Three slants of diphtheria bacilli in 40 cc. of a 2.5% suspension of gum tragacanth	20,000	Intraperitoneally	Survived
1	Three slants of diphtheria bacilli in 40 cc. of a 2.5% suspension of gum tragacanth	20,000	Subcutaneously	Survived

I¹⁷ took advantage of this observation to study the cellular reactions within the peritoneal cavity during the course of peritonitis. From these studies, it was determined that polymorphonuclears constitute the first line of cellular defense and that bacterial phagocytosis by the polymorphonuclears represents the primary and the conspicuous cellular protective reaction on the part of the body.

In order to ascertain the rôle played by the polymorphonuclears and phagocytosis in the animals passively immunized with diphtheria antitoxin, a study more or less similar to that by Snyder and myself was made in these experiments. Total and differential white cell counts of

16. Steinberg and Goldblatt (footnote 14, first reference).

17. Steinberg, B., and Snyder, D. A.: Immune Cellular Reactions in Experimental Peritonitis, Arch. Path. 8:419 (Sept.) 1929.

the peritoneal and peripheral blood were made at short intervals. Peritoneal counts were done by introducing glass capillary pipets through the abdominal wall under sterile conditions and withdrawing the peritoneal fluid. At frequent intervals bacterial counts were made on the peritoneal exudate. The peritoneal, the peripheral cell and the bacterial counts were performed on a normal dog that received by intraperitoneal injection three slants of diphtheria bacilli in 2.5 per cent gum tragacanth to serve as a control for the observations in the passively immunized animal.

In both animals (the control and the passively immunized dog) there was an initial drop of the peripheral white cell count and an

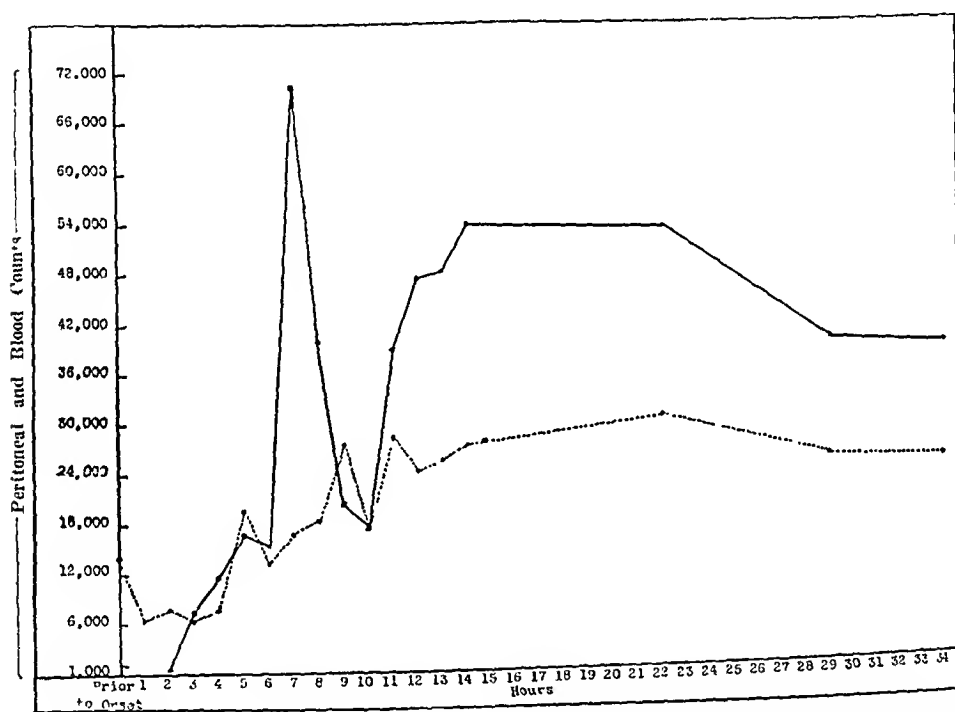


Chart 2.—Blood counts and peritoneal counts in a normal dog given injections intraperitoneally of three slants of diphtheria bacilli in gum tragacanth and injections intravenously of diphtheria antitoxin. The animal survived.

appearance of a small number of cells in the peritoneal exudate. Snyder and I are of the opinion that this initial drop of the total white cells of the blood represents a migration to the inflammatory field and constitutes the first line of cellular defense. There is a gradual rise of the total white cells in the peritoneal cavity of both dogs. The peak of the peritoneal counts in the passively immunized animal is reached at the end of the seventh hour, while in the control dog the peak appears at the end of the fourteenth hour and the total cell count is less than half that of the immune dog (tables 2 and 3; charts 1 and 2). Comparative studies of the peritoneal smears of the control and the

immune dogs (tables 2 and 3) reveal the presence of free bacteria in the exudate of the control dog as late as the eleventh hour (in other control animals, free bacteria were found up to and including the last hour) after the onset of peritonitis, while in the passively immunized dog no free bacteria were seen at the end of the third hour. It was

TABLE 2.—*Blood and Peritoneal Counts in a Normal Dog with Peritonitis Produced by Diphtheria Bacillus*

Hours After Onset of Peritonitis	Blood Count	Differential Blood Count, per Cent				Peritoneal Count	Differential Peritoneal Count, per Cent			Comments on Peritoneal Exudate
		Polymorpho-nuclears	Lymphocytes	Monocytes	Eosinophils		Polymorpho-nuclears	Lymphocytes	Monocytes and Eosinocytes	
Before	13,600	79	12	9	
1	12,550	72	21	8	
2	6,500	60	30	7	3	1,000	100	* Many free bacteria; few polymorphonuclears have many bacteria; many red blood cells
3	6,700	66	24	7	..	No count	100	Same as preceding hour
4	4,900	77	16	6	1	8,150	94	3	3	13,200,000 bacteria per cc.; few free bacteria, most of them phagocytosed
5	5,450	74	22	4	..	8,650	97	1	2	Same as preceding hour
6	5,550	92	4	4	..	8,800	98	2	..	9,600,000 bacteria per cc.; otherwise same as preceding hour
7	6,350	90	5	5	..	22,850	100	5,440,000 bacteria per cc.; occasional free bacterium; many polymorphonuclears with phagocytosed bacteria
8	8,000	87	11	2	..	21,900	98	1	1	No free bacteria; 1 of 30 polymorphonuclears has phagocytosed bacteria; many degenerated polymorphonuclears
9	10,300	93	6	1	..	24,400	99	..	1	Same as preceding hour
11	7,700	87	11	2	..	25,200	98	..	2	3,424,000 bacteria per cc.; bacteria are free and clumped
12	11,350	87	12	1	..	29,800	100	Same as preceding hour
13	14,000	84	16	23,150	97	..	3	1,840,000 bacteria per cc.; otherwise same as preceding hour
14	14,550	91	5	4	..	32,100	100	Many polymorphonuclears with phagocytosed bacteria
22	14,900	92	8	28,800	100	Same as preceding hour
29	14,950	89	8	3	..	15,050	100	No bacteria on culture, few polymorphonuclears with phagocytosed bacteria; dog died on thirtieth hour

apparent that in addition to the neutralization of the toxin by the anti-toxin there were differences in the rapidity of phagocytosis and the number of polymorphonuclears evoked in the two dogs. The passively immunized dog was capable of a more rapid phagocytosis of the invading bacteria and was also able to muster a large and sufficient number of polymorphonuclears to cope with the micro-organisms. A comparison of charts 2 and 3 of an actively and passively immunized animal shows a close similarity in the reaction. As an illustration of a cellular

response in presence of active immunity, peritonitis was produced by *B. coli* in a dog immunized with *B. coli* (Goldblatt and Steinberg¹⁸). The differences between the two animals consisted in the earlier appearance (fourth hour) of large numbers of polymorphonuclears and the considerably greater total number of these phagocytes in the actively than in the passively immunized dog. The rapidity of phagocytosis was alike in both animals. Comparing charts 2 and 3 of the two differently immunized dogs with that of a nonimmune animal (table 2),

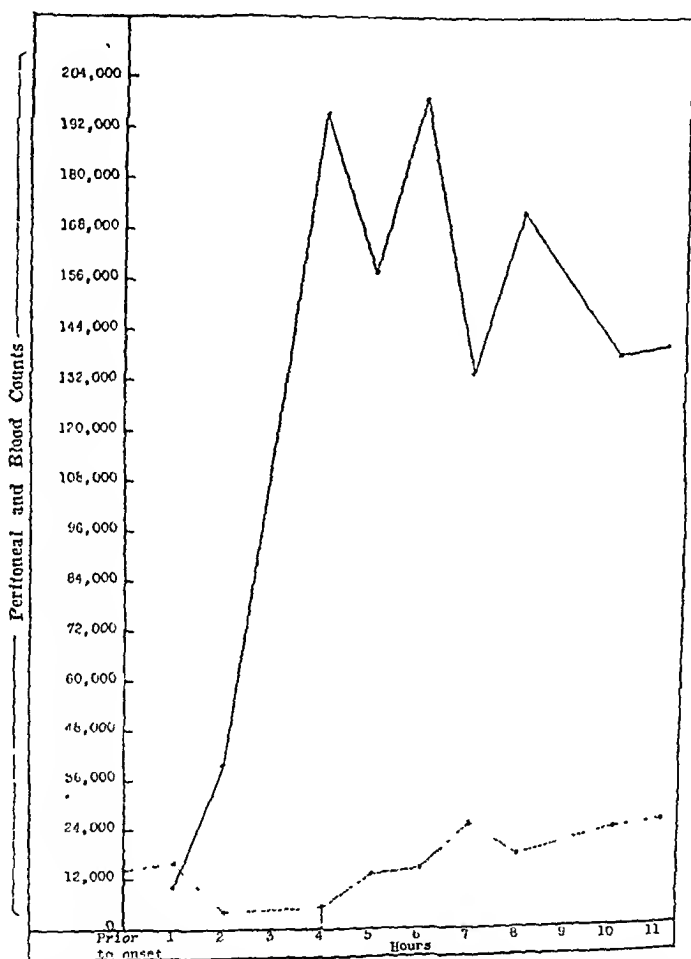


Chart 3.—Blood counts and peritoneal counts in a dog immunized with *B. coli* and given injections intraperitoneally of two slants of colon bacillus in gum tragacanth. The animal survived.

the differences of the time of appearance and the number of polymorphonuclears are quite apparent. The differences are still more striking in the smears of the peritoneal exudate. From the onset of peritonitis to the death of the nonimmune animal, the slides are filled with viable and free bacteria; all the polymorphonuclears are filled to

18. Goldblatt and Steinberg (footnote 14, second reference).

capacity with bacteria, but there are not enough of these phagocytes to take care of all the micro-organisms. On the other hand, in the slides of the immunized animals there are very few free bacteria at the end of the second hour and none at all at the end of the third hour.

TABLE 3.—*Effect of Diphtheria Antitoxin on Blood and Peritoneal Counts of Normal Dog in Which Peritonitis Has Been Produced with Diphtheria Bacilli*

Hours After Onset of Peritonitis	Blood Count	Differential Blood Count, per Cent				Peritoneal Count	Differential Peritoneal Count, per Cent			Comments on Peritoneal Exudate
		Polymorpho-nucleus	Lymphocytes	Monocytes	Eosinophils		Polymorpho-nucleus	Lymphocytes	Monocytes and Eosinophils	
Before	14,000	70	23	4	3	
1	6,550	76	23	1	
2	7,800	80	18	2	..	1,350	100	Bacteria are free and in clumps; polymorphonuclears filled with bacteria
3	6,250	86	10	4	..	7,350	98	2	..	No free bacteria; many phagocytosed bacteria; many new polymorphonuclears
4	7,950	86	12	2	..	11,950	98	..	2	Many broken down polymorphonuclears
5	19,700	89	9	2	..	16,900	100	Same as preceding hour; 3,952,000 bacteria per cc.
6	13,100	84	10	4	1	15,350	100	Few polymorphonuclears with bacteria; none free
7	16,900	93	5	2	..	70,400	100	Same as preceding hour; 4,000,000 bacteria
8	18,600	93	7	40,000	98	..	2	Degenerated polymorphonuclears with bacteria
9	27,200	91	9	20,500	100	Same as preceding hour
10	17,400	89	11	17,600	99	1	..	Same as preceding hour
11	28,550	96	4	38,950	97	3	..	No bacteria in polymorphonuclears
12	24,100	96	4	47,700	96	2	2	Occasional polymorphonuclears with phagocytosed bacteria; 1,132,000 bacteria per cc.
13	25,550	96	4	48,200	98	2	..	Many broken down polymorphonuclears
14	27,400	99	1	54,000	97	3	..	Same as preceding hour
22	30,600	93	6	1	..	53,500	95	2	3	No free or phagocytosed bacteria
29	25,050	96	2	2	..	39,100	95	5	..	Same as preceding hour
34	24,250	92	4	4	..	38,750	94	4	2	An occasional polymorphonuclear with a phagocytosed bacterium
45	21,900	94	6	44,500	97	..	3	Same as preceding hour; no bacterial growth on culture
50	21,300	92	6	2	..	27,000	90	..	10	No bacterial growth on culture
52	12,800	83	14	3	..	14,600	91	9	..	Same as preceding hour; dog survived

Since the survival of the animal with acute diffuse peritonitis is coincident with a rapid phagocytosis and the capacity to evoke a sufficiently large number of polymorphonuclears to cope with the invading bacteria, and the experiments reported here demonstrate that a bacterial toxin plays a deciding part in the death of the animal, it is assumed that in the presence of a sufficient number of polymorphonuclears and a rapid

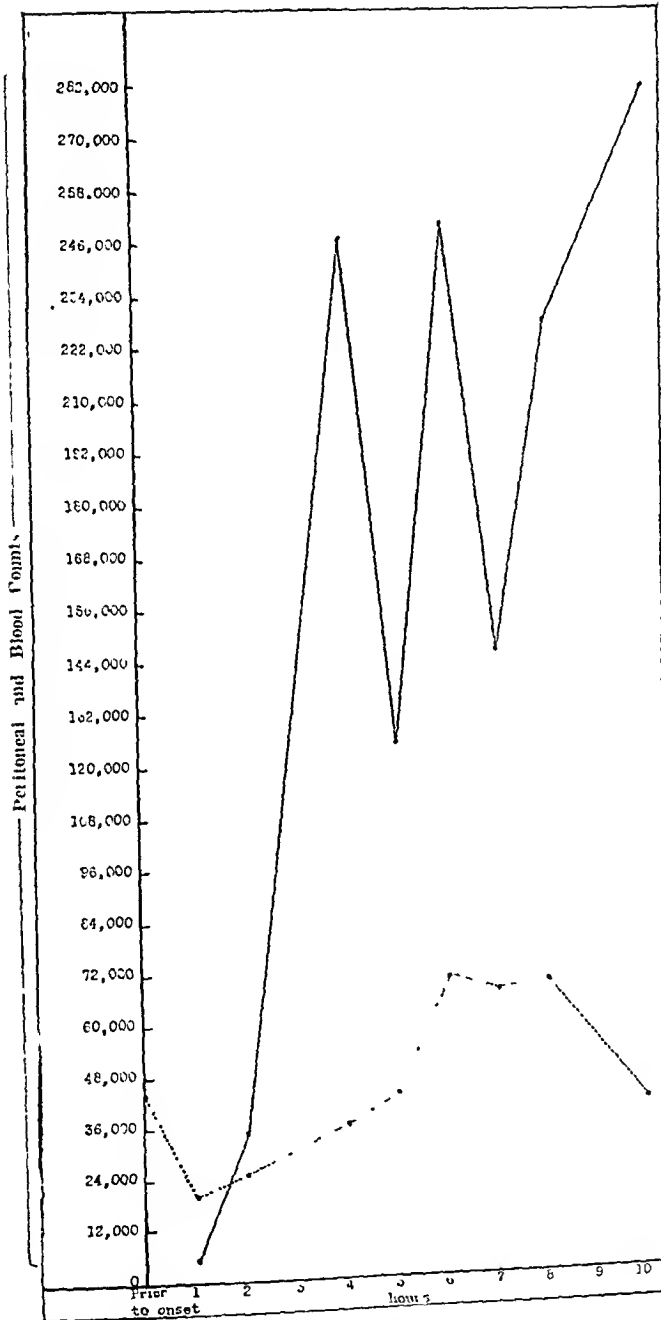


Chart 4.—Blood counts and peritoneal counts in a dog immunized with *B. coli* and given injection intravenously of two slants of colon bacillus in gum tragacanth and injections intravenously of 2 cc. of diphtheria toxin. The animal died ten and one-half hours after injection.

phagocytosis the elaboration of the toxin by the bacteria within the peritoneal cavity is prevented.

The peritoneal and peripheral leukocytosis in the passively immunized animal suggested that the bacterial toxin may inhibit the production or mobilization of polymorphonuclears. Consequently, the administration of the antitoxin neutralized the toxin and removed the cellular inhibitory factor. A dog was immunized with *B. coli* according to the method of Goldblatt and myself,¹⁸ the animal was later given intraperitoneal injections with two slants of *B. coli* in 40 cc. of a 2.5 per cent suspension of gum tragacanth, and at the same time 2 cc. of diphtheria toxin was administered intravenously. Control dogs that

TABLE 4.—*Results in a Dog Immunized with B. Coli and Given Two Slants of Colon Bacilli in Gum Tragacanth Intraperitoneally and 2 cc. of Diphtheria Toxin Intravenously**

Hours After Onset of Peritonitis	Blood Counts	Peritoneal Counts	Comments on Peritoneal Exudate
Prior to onset	44,450	
1	20,050	4,700	An occasional free bacterium; many phagocytosed bacteria; all cells are polymorphonuclears
2	25,550	34,750	Many free and phagocytosed bacteria; all cells are polymorphonuclears
4	36,700	247,200	Many free and phagocytosed bacteria; all cells are polymorphonuclears
5	43,850	125,500	Few free bacteria; many phagocytosed bacteria; all cells are polymorphonuclears
6	70,900	250,000	Few free bacteria; many phagocytosed bacteria; all cells are polymorphonuclears
7	67,600	146,000	A moderate number of free bacteria; all cells are polymorphonuclears
8	68,800	227,750	Few free bacteria; many phagocytosed bacteria; many broken down polymorphonuclears; all cells are polymorphonuclears
10	40,000	281,000	Few free bacteria; many phagocytosed bacteria; many broken down polymorphonuclears; all cells are polymorphonuclears

* The animal died ten and one half hours after the injection.

were similarly immunized with *B. coli* and in which a similar peritonitis was produced with colon bacillus, survived. If a bacterial toxin (diphtheria toxin) inhibits polymorphonuclear formation or mobilization, these phagocytes which ordinarily appear in large numbers in immunized animals will either be diminished in number or totally suppressed. The results of this experiment revealed that diphtheria toxin neither diminished nor inhibited the polymorphonuclear response to an acute diffuse infection of the peritoneum (chart 4). The cellular response was as rapid and as great as in the immune animal without diphtheria toxin (chart 3). However, studies of the peritoneal exudate revealed the presence of free and viable (by culture) bacteria from the first to the tenth hour after the onset of peritonitis in the animal given the diphtheria toxin (table 4). On the other hand, many of the bacteria were phagocytosed. This observation may be suggestive of some

inhibitory or deleterious affect on the polymorphonuclear by the bacterial toxin with a consequent slight to moderate interference with the phagocytic property of the polymorphonuclears.

CONCLUSIONS

In acute diffuse peritonitis, under the conditions of these experiments, death is due to the toxin produced by the bacteria present in the peritoneal cavity. Intestinal paralysis, intestinal stasis and intestinal bacteria, under these conditions, play no part in the death of the animal.

Administration of the corresponding antitoxin averts death in acute diffuse peritonitis.

In the absence of an antitoxin that is capable of neutralizing the toxin, two factors are responsible for the survival of the animal with peritonitis: (1) rapid phagocytosis and (2) a sufficiently large number of polymorphonuclears to cope with the invading bacteria. It is assumed that in the presence of these two factors, the formation of toxin by bacteria is prevented and the death of the animal is averted.

The bacterial toxin has no inhibitory effect on the number or on the rapidity of appearance of the polymorphonuclears. However, the toxin interferes with complete phagocytosis of the bacteria by the polymorphonuclears.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.

ROANOKE, VA.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

AND

ADOLPH A. KUTZMANN, M.D.

LOS ANGELES

KIDNEY

Anomalies.—Braasch¹ observed a number of cases in which the renal pelvis had an anomalous position and form and in some cases was the only clinical evidence of abnormality. When renal anomaly is characterized only by anomalous rotation, the degree of rotation may vary, and may be described by the terms rotation absent, incomplete, reverse and excessive. It does not always involve the entire kidney, but may be confined to one pole and may affect only a segment of the pelvis and the adjacent calices. Although the pelvis may be in the normal position, it is more often observed with either lateral or mesial displacement or with slight ptosis. It is usually situated on a level with the second lumbar vertebra. It may be slightly lower and is then distinguished from ectopic kidney by the fact that its blood vessels take origin at the usual level of the renal artery and vein. It may occur as the result of either congenital or acquired factors; if of congenital etiology, it is referred to as anomalous rotation; if secondary to acquired factors, it is designated as renal torsion.

In fused kidneys, evidence of abnormal rotation is always found, at least in one pelvis, and usually in both. Recognition of fused kidney is made possible largely by demonstration, in the pyelogram, of failure of pelvic rotation. As a result of inability of the fused kidney to rotate, the renal pelvises remain situated on the anterior aspect of the kidney. The calices usually extend anteriorly, mesially or laterally, and often are clubbed terminally. The ureteropelvic juncture may be

1. Braasch, W. F.: Anomalous Renal Rotation and Associated Anomalies, *J. Urol.* **25**:9 (Jan.) 1931.

situated either on the anterior aspect of the pelvis or on its lateral or mesial border.

Failure of the embryonic kidney to make its normal ascent results in congenital renal dystopia or ectopic kidney. The kidney usually is abnormal in structure, and, as a result of failure of rotation, the pelvis is situated anteriorly and is bizarre in outline. The renal blood vessels are usually abnormal in number and arrangement and often influence the anomalous shape and position of the kidney and its pelvis.

The clinical diagnosis of anomalous rotation is possible only by means of pyelography. Evidence of renal rotation may be observed with clinical conditions in which it may be difficult to determine whether the rotation was primary or secondary.

Abnormal rotation of the kidney observed as the result of other than congenital factors is known as renal torsion. It may result from displacement from either extrarenal or intrarenal pathologic conditions, renal ptosis, postoperative deformity and injury. As a result of torsion, the kidney may be displaced in any direction and its axis changed to various angles. The pyelogram usually will reveal pelvic rotation, varying from a slight difference in the axis of one or more calices to complete reversion of the pelvic arrangement. As a result of marked renal ptosis, or from displacement by extrarenal tumor, the renal pelvis may assume a position and contour suggestive of ectopic kidney.

In pyelographic examination occasionally a renal pelvis is observed the shape of which is suggestive of congenital deformity; this is termed an embryonic pelvis. Its outline is characterized by an elongated pelvis, from which a series of abbreviated calices extend laterally, anteriorly or mesially, at comparatively regular intervals. It may be associated with a variable degree of abnormal rotation. Although the kidney is sometimes in a normal position, there may be a variable degree of dystopia, and there is usually some evidence of incomplete rotation. Surgical exploration may reveal that the kidney is abnormal in shape and size; it may be comparatively elongated, and often there is marked evidence of fetal lobulation.

It is known that an anomalous kidney is more often affected by lesions than a normal kidney. Hydronephrosis and stone are the lesions most commonly found and may be the direct results of anomaly. Symptoms suggestive of nephralgia frequently are associated with an anomalous renal position.

Lazarus² stated that one of the most common anomalies of the genito-urinary system is that of supernumerary or double ureter. The

2. Lazarus, J. A.: Heminephrectomy for Calculus Pyonephrosis in a Case of Bilateral Duplication of Ureters and Pelves, *J. Urol.* **24**:503 (Nov.) 1930.

pelves associated with complete reduplication of the ureter are usually of unequal size and configuration. The upper pelvis is the smaller and possesses fewer calices. Although the capacity of the pelvis is unequal, the segments usually have equal functional activity. The ureters as they leave the pelvis lie close together and are usually connected by strands of connective tissue. They terminate in the lateral trigonal angle in such a way that one ureteral orifice lies just above the other. The upper one corresponds to the lower pelvis and the lower one to the upper pelvis. The upper pelvis is usually the smaller of the two.

Lazarus reported a case of bilateral duplication of the ureters in which heminephrectomy was performed. At operation the kidney was elongated and consisted of two portions separated by a shallow groove running across the anterior surface of the renal mass. The upper portion, which comprised about two thirds of the entire mass, appeared normal and contained a small intrarenal pelvis with a diminutive ureter; the lower third was represented by a pyonephrotic sac containing small calculi with a dilated pelvis and ureter. The blood supply of the lower pole appeared to arise as branches of the main renal pedicle which passed to the upper hilus. These branches coursed downward over the anterior surface of the pelvis to enter the hilus of the sac anterior to the pelvis. After the kidney had been completely mobilized, the ureters were isolated and freed from their adhesions of connective tissue, and the blood supply of the lower renal portion was clearly defined. The vessels were doubly ligated and divided. The dilated ureter was then divided. The lower pyonephrotic portion of the kidney was amputated just above the groove, a good wedge of the healthy kidney being taken with it. Bleeding was brisk, but was easily controlled with clamps and ligatures. Two large strips of muscular tissue were laid across the cut end of the kidney and six mattress sutures were used to close the rent, the tissue being incorporated within them. Following decapsulation, a flap of perirenal fat was loosely stitched over the sutured pole of the kidney, and a rubber tube and dam were placed below this for drainage. The wound was closed about the drains in layers.

The postoperative course was uneventful. At no time was there any urinary leakage. The patient left the hospital on the twenty-third postoperative day with the wound solidly healed.

[COMPILERS' NOTE.—On first thought, resection of the diseased segment of a double kidney seems to be a formidable procedure. When conditions are favorable, however, it offers no great technical difficulties and is followed by favorable results. Heminephrectomy should not be attempted unless the pathologic condition is confined entirely to one segment and clinical evidence shows definitely that the remaining seg-

ment is normal and functioning. Even under such favorable circumstances infection may invade the remaining segment, necessitating a secondary operation. With proper suturing, the postoperative hemorrhage should be negligible. If infection remains in the tissues, however, a sinus may persist indefinitely and reopen at intervals. The healing process resulting after heminephrectomy was clearly shown in a case reported by Braasch and Scholl in which the remaining segment of a double kidney was subsequently removed. The resected surface, although pitted in some areas, was smooth, and had assumed the normal rounded contour of one of the renal poles. The pathologic process had involved only the tissues immediately adjacent to the line of incision. There was moderate lymphocytic infiltration in some areas, possibly caused by absorbed suture materials. The glomeruli were somewhat clumped and the destruction of interglomerular tissue was greater than that of glomeruli. There was only slight fibrosis and hyalinization of the glomeruli, and many immediately adjacent to the line of incision were apparently normal. Factors rendering the operation easier and favorably influencing the results are: (1) the considerable distance separating the two pelves; (2) a definite division of the two segments by a cicatricial band, and definite confinement of the disease to one segment, and (3) the chronic and cicatricial nature of the pathologic lesion.]

Bumpus³ cited the case of a young woman whose pyelogram, made at the Mayo Clinic in August, 1928, showed evidence of two pelves, one anterior to the other, due to longitudinal instead of transverse division. A pyelogram of the opposite kidney was obtained three days later and indicated that this kidney was normal. The divided functional test showed a 10 per cent return of the dye from each kidney in fifteen minutes.

In Young's experience the pelves of a double kidney are always situated one above the other, the division being transverse, but in the report of a case of duplication of the renal pelvis Potter and Sexton stated that the division may be longitudinal through the kidney with one pelvis anterior and one posterior.

Lafitte⁴ observed a case of congenital pelvic kidney during pregnancy. He mentioned that these anomalies are not common, although Girard in 1911 reported 102 cases. They are the most common anomalies of position of the kidney. Congenital pelvic kidney may be situated more or less high, sometimes at the entrance of the small pelvis or

3. Bumpus, H. C., Jr.: Unusual Duplication of Renal Pelvis, *J. Urol.* **25**:39 (Jan.) 1931.

4. Lafitte: Ectopie pelvienne congénitale du rein observée au cours d'une grossesse, *Bull. et mém. Soc. nat. de chir.* **56**:910 (July 12) 1930.

entirely in the pelvis itself, being found in the concavity of the sacrum, or it may lie on the pelvic floor. When the kidney lies at the level of the entrance of the pelvis, the organ may constitute a decided obstacle to the ascension of the pregnant uterus and to the normal mechanism of delivery; it may narrow the pelvis more than 3 cm. Such a kidney is usually fixed; it is only partially mobile, which is indicated by possible torsion on its axis. The possibility of fixing it higher has been considered but rejected; it cannot be transported either to the lumbar region or to another situation in the pelvis where its presence would not be such a marked obstacle to normal pregnancy. The value of the corresponding kidney should be estimated. Nephrectomy may be indicated in a few cases. If the kidney is healthy and the pregnancy has advanced two months, Lafitte advised waiting until full term before intervention. In some cases, operation may be carried out just before childbirth. Girard reported a series of cases of pregnancy and ectopic kidney. Four patients were operated on during pregnancy and 9 during labor; abortion occurred in 13 cases. If ectopy was not complete, delivery was spontaneous but painful and prolonged.

[COMPILERS' NOTE.—Ectopic kidneys in general are prone to the development of pathologic states. They may produce dystocia when they lie at or below the pelvic rim. If the uterus has been able to rise above the pelvis into the abdomen and interference with the descent of the fetus at term takes place, the rare indication for cesarean section may arise, particularly if the ectopic kidney is known to be functioning normally. As Girard, quoted by Lafitte, pointed out, abortion will be the most common outcome.]

Tumors.—Busser⁵ concluded from a study of 94 cases of primary epitheliomas of the kidney that it is impossible to judge the histologic structure of carcinoma of the kidney by its gross appearance. From a macroscopic point of view, carcinomas of the kidney present a picture as follows: a partial nodular form with preservation of some normal renal tissue; a massive nodular form; rarely, an infiltrated form; and a cystic form, which is always localized at the lower pole. Epitheliomas are divided into two groups, epitheliomas of renal origin and undifferentiated epitheliomas. The renal type is tubular and trabecular; the undifferentiated type is alveolar and trabecular. Between these two types are found many different transitory types showing the transition of the first type into the second one. Busser expressed the opinion that

5. Busser, F.: Étude anatomique des épithéliomes primaires du rein de l'adulte; à propos de 94 observations, Bull. de l'assoc. franç. pour l'étude du cancer, 19:198 (March) 1930.

the theory of the hypernephroma is a fallacious one; all epitheliomas of the kidney are of renal origin.

[COMPILERS' NOTE.—Busser's grouping is somewhat similar to that of Ewing, who divided tumors of the kidney into two main groups, papillary adenocarcinomas and alveolar carcinomas. In a series of cases reported from the Mayo Clinic in which nephrectomy was performed for tumor, the major portion belonged to the first group of papillary adenocarcinomas. These tumors, usually considered as the hypernephroma group, are the most common of renal tumors. As a rule they are only moderately malignant, not infrequently existing for years without causing symptoms. They generally become large, bulky and hemorrhagic, and cause marked distortion of the renal contour. They occurred in 152 (82.5 per cent) of 184 cases. Thirteen (8.5 per cent) of the patients died following operation, 23 were not traced after operation and 57 (53.8 per cent) of the remaining 106 were living and well on an average of six years after operation.

The second group, or alveolar carcinomas, form only a small proportion of renal tumors. They are homogeneous and whitish, and at times diffusely infiltrate the renal tissues. They are highly malignant, early invading the pelvis and breaking through the renal capsule. Hemorrhage and the formation of cysts are rare. Histologically these tumors tend to reproduce the tubules of the adult kidney, resembling the renal parenchyma. The structure varies from that of well formed alveoli to areas in which there is little differentiation, the cells being matted together with only a small amount of intervening stroma. There were 32 cases of alveolar carcinoma in the series. Five (15.6 per cent) of the patients died following operation; 4 patients were not traced, and only 3 (13.4 per cent) of the remaining 23 were still alive. These three patients were living on an average of ten years after nephrectomy.]

Kretschmer and Hibbs⁶ studied 17 cases of malignant tumors of the kidney which occurred in infants and children. Such tumors are rare; Bugbee and Wollstein, in a review of 4,903 necropsies on infants and children, did not report a case of malignant renal tumor.

Wilms showed that mixed tumors of the kidney are composed of a variety of different tissues; that all the tissues develop from a cell tissue that does not show any of the known differentiating marks. Glandular elements are always present, and smooth and striated muscle, cartilage, fat and elastic, fibrous and myxomatous tissue are usually present.

6. Kretschmer, H. L., and Hibbs, W. G.: Mixed Tumors of the Kidney in Infancy and Childhood: A Study of Seventeen Cases, *Surg. Gynec. Obst.* 52:1 (Jan.) 1931.

Embryonal tumors of the kidney are the most common primary neoplasms that occur in children. The largest tumor in Kretschmer's series weighed 1,530 Gm. and the smallest, 235 Gm.; the average weight of all of the tumors was 762 Gm. The tumors are predominately unilateral; only 2 of the 17 reported were bilateral. They are encapsulated and retroperitoneal, and arise within the renal capsule. They are globular to oval in shape, solid, opaque and variously subdivided into lobules. Somewhere on the surface a nodule of renal tissue usually remains. The most distinguishing feature of these tumors is their embryonal structure, with a variety of tissue of abortive renal elements. The types of cells and the amount vary in the different tumors. They are usually myxomatous tissue composed of masses of polymorphous, nucleated cells in which are embedded glandlike or ductlike figures resembling uriniferous tubules, which may be sparse or abundant. There are both epithelial and connective tissue elements. The epithelial elements consist of small and large undifferentiated cells which^a are often spoken of as epithelial cell nests and embryonal tubules. The connective tissue elements consist of loose stroma, undifferentiated round cells and striated and nonstriated muscle fibers.

Extensions and metastases of such tumors are exceptional unless the original tumor is large. Regional involvement by extension is the usual method of growth. Extension and metastasis may occur throughout the entire abdomen. The time that elapsed between the first noticeable symptoms and the physician's examination was usually short; this varied from six days in one case to twelve months in another. Gross blood in the urine was not found in any of these cases. An increase of temperature is often found with malignant tumors in the adult; fever was present in 9 of the 17 cases, and in all a palpable tumor was present. In all but 1 case, the presence of the tumor was directly responsible for the patient's seeking medical attention. Albumin was present in 7 cases; microscopic blood was found in only 1 case. In every case there was definite evidence of secondary anemia. Of the 17 patients, 16 died.

Bowen and Bennett⁷ stated that squamous cell carcinoma of the renal pelvis is not common; among the malignant tumors arising from the epithelium in this region, it is much less common than the papillary types. In 1927, 35 cases of renal tumor were reported from Peter Bent Brigham Hospital; 5 of the tumors originated in the pelvic epithelium; 2 of these were associated with other types of growth, a third was of the papillary type, but none was associated with stone.

7. Bowen, J. A., and Bennett, G. A.: Squamous Cell Carcinoma of the Kidney Pelvis, *J. Urol.* **24**:495 (Nov.) 1930.

At the time of the report, 9 of the 35 patients were alive, and only 1 of these, with the papillary type of tumor, had suffered from a growth in the renal pelvis.

Bowen and Bennett reported the case of a man, aged 57, with squamous cell carcinoma of the renal pelvis. For many years urinary infection, and for at least a year a renal stone, appeared to be present. Operation revealed moderate pyonephrosis, a branching stone and tumor of the renal pelvis. A recurrence was noted several months later. This case emphasizes the danger of neglecting urinary infections.

[COMPILERS' NOTE.—Squamous cell tumors of the renal pelvis probably result, in most cases, from chronic irritation; they are highly malignant, rapidly involve the renal parenchyma and neighboring tissues and metastasize readily. This type of growth is sometimes, as in Bowen and Bennett's case, associated with renal calculi, which may be rough, irregular and very large. Owing to the absence of symptoms suggestive of a malignant condition, these tumors are rarely seen when the growth is small or localized to the renal pelvis. The operative mortality is high, and most patients who survive die shortly after the operation from local recurrences, or metastatic growths.

Four of 5 cases of squamous cell tumors of the renal pelvis observed at the Mayo Clinic between 1907 and 1922 were associated with renal stone; the calculi in 3 kidneys were extremely large and of the staghorn type. One patient died eight days after operation, and 3 died during the first four months. The fifth patient was alive without symptoms of recurrence six months after operation.]

Graham⁸ stated that renal neoplasms occur at all ages, more than 50 per cent occurring in the fourth and fifth decades. The type of tumor of the kidney described by Grawitz is the most common and the most significant. Hypernephroma rarely occurs in children, but is the prevailing type of renal neoplasm in adult life. It is observed more frequently in men than in women. It may be situated in any part of the kidney, but is most often in the upper pole. It is rarely bilateral. Many of the smaller lesions are partially or completely encapsulated. In such cases the tumor increases by local growth without invasion of the surrounding renal tissue. The renal parenchyma may become atrophic as the result of compression. On gross examination, hypernephromas may appear as circumscribed, encapsulated, or diffusely infiltrating masses. They are usually soft and light yellow, and are frequently complicated by varying degrees of diffuse hemorrhage and necrosis.

8. Graham, Allen: Pathology of Renal Tumors, *Radiology* 15:531 (Nov.) 1930.

Second in order of frequency and significance among renal neoplasms are carcinomas, which may be considered in two groups: those arising from tubular or glandular epithelium and those arising from the pelvic mucosa. Adenomas are not infrequently encountered at necropsy as single or multiple lesions in one or in both kidneys. They are generally small, white, circumscribed, nonencapsulated nodules not exceeding 1 cm. in diameter. When the adenoma becomes malignant, fairly well circumscribed or diffusely infiltrating, neoplasms of considerable size may result. Carcinoma of the kidney in childhood is usually a different type and apparently has a different origin from carcinoma in adults. It is generally more undifferentiated or embryonal, and in many cases it seems to be teratomatous, with one type of tissue predominant. The growth may be rapid and large tumors may form, but with little tendency to distant metastasis. Carcinomas arising in the renal pelvis are of two types, papillomatous and epidermoid. A true epidermoid carcinoma with keratohyaline material and pearl formation may arise in the pelvis of the kidney, the seat of leukoplakia. The kidney is infiltrated, and the usual mode of metastasis is through the lymphatics. These tumors are relatively infrequent; they are usually found in chronically infected kidneys or in association with calculus.

True sarcoma in the sense of a malignant tumor arising from the supporting tissue is rarely observed in the kidney as a primary tumor. A search of the records of the Cleveland Clinic for the last eight years failed to disclose a case.

Mixed tumors, the third type of renal neoplasms in order of frequency and significance, are not homogeneous and do not conform to type. Usually they grow rapidly, form large, clinically detectable masses, are difficult to distinguish from pararenal, retroperitoneal and intraperitoneal tumors, and show little tendency to disseminate distant metastasis. On microscopic examination, their structure is found to be extremely variable. The tissues are rarely of a single uniform type. Many of the tumors are radiosensitive and may be kept under control for a considerable period by the application of roentgen rays. The response to irradiation depends, as in the case of tumors generally, on the degree of undifferentiation. Metastatic and recurrent tumors also are radiosensitive in some instances.

Roentgenograms of the kidney indicate the relative size, position and contour of the organ, and show relative variations in the density of the shadow of one portion of the kidney as contrasted with that of another, or of the kidney as contrasted with its surroundings. The cooperation that has been established between urologist and roentgenologist accounts in great measure for the high degree of accuracy

achieved in the interpretation of variations from the roentgenogram and pyelogram of the normal kidney.

Patch and Rhea⁹ studied the pathogenesis of bleeding of renal tumors. In the examination of serial sections they were unable to demonstrate destruction of the lining of the pelvis by a tumor, and felt justified in concluding that the hematuria resulted from widely dilated, thin-walled blood vessels in the subepithelial connective tissue of the small protrusion into the superior calix.

Tuberculosis.—Spitzer¹⁰ stated that the absence of the bacillus of tuberculosis in the secretion from a kidney does not mean that tuberculosis of the kidney does not exist. The presence of the bacillus in the urine indicates that a focus of tuberculosis is present in either the genital or the urinary tract, as these bacilli do not pass through normal renal epithelium. The experience of careful observers has demonstrated that there is a better chance that patients with tuberculosis of the kidney will recover from other conditions, if the diseased kidney is removed. Tuberculous lesions elsewhere in the body are not a contraindication to nephrectomy; in the majority of cases these are improved after nephrectomy. Regional and spinal anesthesia should be used when possible.

Progressive illness and eventually death are the rule in cases in which nephrectomy cannot be performed for tuberculosis of the kidney. The excellent results obtained following nephrectomy in well selected cases of renal tuberculosis warrant and make imperative its practice whenever possible. If nephrectomy is performed the remainder of the genital and urinary tracts rarely become infected, whereas when nephrectomy is contraindicated, the other parts of such tracts frequently become tuberculous. Other treatment than nephrectomy for tuberculosis of the kidney is not known.

[COMPILERS' NOTE.—That tuberculous bacilluria may exist without renal tuberculosis finds fewer and fewer advocates in the literature. The question of whether nephrectomy is always the procedure of choice in unilateral renal tuberculosis, which was formerly almost universally accepted, is not so easily answered. Thomas has provided much to think about on this subject during the last few years. Perhaps in a few early cases that can be carefully controlled under hospital conditions from month to month, medical treatment may be advisable. However, Spitzer undoubtedly voiced the general opinion in advocating early

9. Patch, F. S., and Rhea, L. J.: On the Pathogenesis of Bleeding in Tumours of the Kidney, *Brit. J. Urol.* **2**:248 (Sept.) 1930.

10. Spitzer, W. M.: Indications and Contra-Indications for Nephrectomy in Renal Tuberculosis, *J. Urol.* **24**:469 (Nov.) 1930.

nephrectomy in these cases. When performed early, nephrectomy obviates spread of the infection to other parts of the urinary tract, and in the majority of cases definite cure can be established. In the presence of genital tuberculosis, and especially of bilateral renal tuberculosis, surgical procedures are not nearly so definitely indicated.]

Actinomycosis.—Recht¹¹ stated that there are only 8 reported cases of actinomycosis of the kidney. Israel reported 2 cases. Stanton, Kunitz and Kleinschmidt each reported a case in which actinomycotic processes were not present elsewhere. In 2 cases reported by Earl and Abbott there were processes in the brain, lungs and spinal column in addition to those in the kidney. Stanton's and Earl and Abbott's cases were proved at necropsy; the remainder were identified at operation. In Cohn's case actinomycotic spores were found in the urine associated with pyelonephritis and prostatitis. It was thought that infection took place as a result of trauma.

Recht cited the case of a man, aged 65, with arteriosclerosis, chronic nephritis and cystopyelitis. The patient died, and at necropsy actinomycotic nephritis with abscess was found. Search for a primary focus revealed an abscess in the cuneiform bone. The infection of the urinary tract was thought to have been carried to the kidney by the blood stream.

In primary renal actinomycosis Recht noted certain characteristics which later seemed to disappear. The actinomycotic process localized first in the medullary portion of the kidney. General actinomycosis followed, and later the kidney became infected. Cortical abscesses were noted before involvement of the medullary portion.

[COMPILERS' NOTE.—The rarity of renal actinomycosis as a primary or a secondary disease is emphasized. The diagnosis will rest on finding the ray fungus in the urine, or in the tissues at operation. Eisendrath expressed the opinion that operation is contraindicated unless the lesion is well encapsulated; he recommended Bevan's treatment with copper sulphate, potassium iodide and roentgen rays. Three primary cases are on record in which the cure is of long standing (Eisendrath). A single case of primary actinomycosis of the ureter has been noted in the literature (Eisendrath).]

Movable Kidney.—Lewis and Carroll¹² stated that every kidney is normally movable, making its excursions up and down with respiration or with movements of the body. The kidney becomes diseased when

11. Recht, Hans: Zur Kenntnissnahme der "isolierten" Nierenaktinomykose, Deutsche Ztschr. f. Chir. **224**:414 (June) 1930.

12. Lewis, B., and Carroll, G.: Clinical Evidence on the Question of Movable Kidney, J. Urol. **24**:479 (Nov.) 1930.

mobility is extreme, or when it becomes displaced and remains in its abnormal position.

Movable kidney demands prompt recognition and appropriate surgical relief. Diagnosis requires proof particularly as to whether the symptoms are from displacement or mobility. Methods of relief are palliative and surgical. Nephropexy affords permanent results when properly carried out. Binders do not cure or afford permanent relief. Fattening methods of treatment are not successful.

Deming¹³ stated that nephroptosis is a common condition, but is not always accompanied by symptoms. The coexistence of visceroptosis with nephroptosis is rare; disease of the gallbladder is sometimes associated with movable kidney. Kinks of the ureter are secondary to ptosis, and renal infection occurs in 33.33 per cent of the cases. Conservative treatment is effective in some instances. Deming has devised a new and successful extraperitoneal operation for nephroptosis which does not injure the kidney or its capsule and which utilizes all the natural supporting structures and places the kidney in an anatomically correct position.

Hydronephrosis.—Scholl¹⁴ stated that the present tendency of urologic surgeons is to employ the most conservative methods in the treatment for lesions of the kidney whenever such measures are compatible with satisfactory results. It is now possible to utilize the less radical procedures, with the consequent saving of functioning tissue. These procedures are especially applicable in lesions such as bilateral hydronephrosis.

A case is reported in which operation was performed for bilateral hydronephrosis. Nephropexy and decapsulation, with stripping of the renal vessels and freeing of the ureteropelvic angle, were performed on both kidneys. Immediately after operation the pelvic capacity and retention were within normal limits. The patient was active physically, doing a full day's work and living a normal life free from pain or discomfort more than a year after operation. The urine from the bladder contained only a few pus cells and no albumin. The patient had gained more than 50 pounds (22 Kg.) in weight.

Surgical Technic.—Holland¹⁵ presented a method of nephrostomy which Cabot has found useful and which has the following advantages:

13. Deming, C. L.: Nephroptosis, Causes, Relation to Other Viscera, and Correction by a New Operation, *J. A. M. A.* **95**:251 (July 26) 1930.

14. Scholl, A. J.: Conservative Surgery of Bilateral Hydronephrosis, *J. Urol.* **24**:251 (Sept.) 1930.

15. Holland, W. W.: A New Method of Performing Nephrostomy: Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **5**:325 (Nov. 12) 1930.

The nephrostomy tube can be introduced without mobilization of the kidney; it can be quickly and accurately placed in the pelvis with the minimal amount of trauma, and intrarenal hemorrhage can be controlled through pressure of the tube. A uterine probe is bent into a V shape, introduced into the incision in the pelvis, and brought out at the point of election on the convex border of the renal cortex. The uterine probe is used because of its bulbous end and its malleability. A piece of stout thread is attached to the end of the probe which is drawn down and out through the incision in the pelvis and attached to a winged catheter.

Cabot stated that the central requirement of this method is that the tube shall be accurately placed in the renal pelvis without undue destruction of the substance of the kidney. The operation is commonly applied to patients for whom the element of time is important. The common method has been to insert an instrument through the kidney until it is thought to lie in the pelvis of the kidney. By the procedure described, no difficulty is experienced in introducing the tube into the pelvis. It is not necessary to deliver the kidney to perform the operation. A small opening is made in the pelvis, and the probe is introduced and pushed out through the cortex at the point of election. There is no certain point of election to be used as a standard. The tube should come out at the point where it will best drain the kidney. The common complication of nephrostomy is bleeding from the wound. Bleeding may be stopped by pressure. If the hole is larger than the tube, clots may form in the pelvis and thus the whole operation is a failure. By this method the V-shaped end of the catheter slips easily into the hole and the tube fits so snugly that bleeding is entirely controlled. The tube will stay in position as long as necessary. The second great difficulty in the old method comes at the time of insertion of another tube. A tube may be required for months or even permanently. This type of catheter will remain anchored and when a fresh tube is put in it returns with certainty to the original position.

[COMPILERS' NOTE.—Nephrostomy by incision through the renal cortex into the pelvis and subsequent drainage by catheter has too often been marred by hemorrhage into the pelvis. As this procedure interferes with renal function, its purpose may be defeated. Cabot's operation, as described by Holland, seems to offer several advantages in that the kidney need not be disturbed from its bed, a small exposure of the pelvis is necessary, the opening in the parenchyma is made just large enough to admit the catheter, which fits snugly, and the catheter can be accurately guided into the proper position for drainage.]

Solitary Kidneys.—Walters and Wright¹⁶ reviewed 52 operations on solitary kidneys and ureters performed at the Mayo Clinic over a period of nineteen years. Solitary kidney occurred twice as often in men as in women; in 75 per cent of the cases patients were in the third or fourth decade. In 45 of the 52 cases, operations were performed for the removal of urinary calculi; in the 7 remaining cases, for conditions other than stone. Of the 45 cases of lithiasis, the stone was removed from the kidney in 34 and from the ureter in 11. There were 6 deaths following removal of stones from the kidney, a mortality of 13.3 per cent. All of the 11 patients from whom stones were removed from the ureter of a solitary kidney recovered. Of these patients, 4 had complete urinary obstruction, and 2 had had anuria, lasting for twenty-four hours after admission. In cases in which operation was performed for stone, pelviolithotomy was done in 24 instances, ureterolithotomy in 10, nephrolithotomy in 7, nephropelviolithotomy in 2, pelvio-ureterolithotomy in 1 case, ureteral meatotomy in 1, and resection of the upper pole of the kidney with removal of stones in 1.

The risk of operation on the solitary kidney is dependent on its function and the degree of infection. Renal function was abnormally low in all of the cases. Delay in operating on a solitary kidney until urinary obstruction with anuria had occurred definitely increased the mortality rate of operations in such cases. Results are somewhat dependent on the size and number of stones present. Reports in the literature and a study of cases seen at the clinic would indicate that in the presence of satisfactory function of the remaining kidney, without abnormal infection, multiple operations can be safely undertaken on the solitary remaining kidney, with the expectation of satisfactory results.

[COMPILERS' NOTE.—The conclusions in a recent paper by Keyes and Mathé on solitary kidneys and ureters are, in general, in agreement with those of Walters and Wright, who have emphasized that the expectancy of good results in operative procedures is dependent on renal function and the degree of infection. It has been shown experimentally that a fourth of the renal parenchyma may adequately take care of renal function, if the remaining tissue is healthy and in condition to function so far as its vascular supply and physiologic drainage are concerned. The urgency for early operation is easily understood in the light of this experimental evidence.]

16. Walters, Waltman; and Wright, William: Operations on Solitary Kidneys and Ureters: Report of Fifty-Two Cases, *Surg. Gynec. Obst.* **51**:836 (Dec.) 1930.

Mathé¹⁷ stated that the treatment for stone in the solitary kidney and ureter includes such prophylactic measures as the early removal of unilateral calculi and nephrectomy for pyonephrosis due to calculus which might act as a focus for the formation of stone in the healthy kidney, the clearing up of all foci of infection in other portions of the body, the elimination of stasis in the upper and lower parts of the urinary tract, the eradication of infection in the remaining kidney, and a careful regimen with regard to abstinence in eating and drinking.

Five cases of stone in a solitary kidney are reported, the clinical cause of which emphasizes early removal of stone from the single kidney before renal insufficiency and advanced infection have set in and increased the surgical risk. Early lithotomy on the solitary kidney and ureter is a benign operation, followed by practically no shock, and is tolerated as well as by patients with two kidneys. Attempts to induce stones to pass from a solitary renal pelvis or ureter by cystoscopic manipulation are dangerous because the stone, in passing, may obstruct the ureter. Surgical removal of stone from a solitary kidney and ureter requires the most exacting operative technic and keen surgical judgment. Preliminary drainage and lavage should be made through the ureteral catheter. A wide incision assures good exposure. Extreme gentleness should be employed in handling the kidney, blood vessels should not be sacrificed, and the incision in the pelvis and ureter should not be sutured, in order to assure drainage. A combination pyelotomy and nephrotomy incision permits entire removal of a stone and is less likely to be followed by recurrence. Decapsulation should be done to avoid postoperative renal congestion.

URETER

Tumors.—Cerati¹⁸ studied 76 cases of primary epithelial tumors of the ureter; 55 were papillary tumors and 17 were nonpapillary; the nature of the neoplasm could not be determined in 5 cases. From a clinical point of view these tumors are divided into three groups: those situated low, those in the median and superior portions of the ureter and those in both ureters. The evolution depends almost entirely on the histologic type of the tumor. Even in histologically benign tumors the prognosis is serious on account of the accompanying renal lesions. The diagnosis is difficult. Cystoscopy is important because it permits observation of the tumor (visible in a third of the cases),

17. Mathé, C. P.: The Management of Stone in the Solitary Kidney and Ureter, *Surg. Gynec. Obst.* **52**:79 (Jan.) 1931.

18. Cerati, P.: Contribution a l'étude des tumeurs épithéliales primitives de l'urètre et de leur traitement, *Montpellier méd.* **45**:126, 1930.

bilateral ureteral catheterization and biopsy. Ureterograms sometimes give definite evidence of the growth of the tumor. Nephro-ureterectomy is the treatment of choice when the corresponding kidney functions satisfactorily and the general condition of the patient permits. If complete nephro-ureterectomy cannot be performed, one of several other procedures may be indicated, such as low resection of the ureter outside or through the bladder with ureteroneocystostomy, resection with suture end to end, or fixation to the skin, transvesical resection of a pediculated tumor or diathermization by the endovesical route.

Ockerblad and Helwig¹⁹ stated that primary carcinoma of the ureter is rare; Meeker and McCarthy reviewed only 33 cases up to 1923. Kretschmer reported a case in 1922. Ochsner had reviewed 47 cases of primary tumor of the ureter, both benign and malignant. Since 1923, Ockerblad and Helwig have reviewed approximately 18 cases and reported a case of their own. Primary carcinoma of the ureter is still a rare disease, but owing to increasingly careful necropsies and skillful urologic diagnosis, more cases continue to be reported. If the growth in the ureter is discovered in its early stages, successful operation and cure are not impossible. The symptoms are obscure and variable; hematuria is a reliable symptom. The diagnosis can be made by a ureterogram which shows a dilation or filling defect in the ureter.

[COMPILERS' NOTE.—A primary malignant growth in the ureter is rare. The distinction of secondary neoplasms from the renal pelvis and also from inflammatory granulomas, as described by Braasch, may offer difficulties even with cystoscopy and ureterography. Hematuria, a localized filling defect shown in the ureterogram, and ureteral and pelvic dilatation, constitute the three most reliable criteria in diagnosis. As Cerati pointed out, the ureterogram may sometimes appear normal. Complete nephro-ureterectomy, dissecting out the ureter first (Beer), is the ideal treatment. If the tumor has grown into, or has been transplanted into the bladder, one gains additional diagnostic evidence and the surgical attack is directed first on the bladder and the lower part of the ureter. Here ureteroneocystostomy or transplantation of the proximal portion of the ureter into the skin may be necessary at the primary operation.]

Rohrer²⁰ reported a case of primary papillary epithelioma of the ureter, in which there were typical symptoms. Implants occurred from above downward, in the direction of the urinary stream. When nephrec-

19. Ockerblad, N. F., and Helwig, F. C.: Primary Carcinoma of the Ureter, *J. Urol.* **24**:451 (Nov.) 1930.

20. Rohrer, P. A.: Papillary Epithelium of the Ureter, *J. Urol.* **24**:639 (Dec.) 1930.

tomy is contemplated for renal papilloma or tumor in the upper part of the ureter, it is advisable to remove the ureter in toto, either at the time of nephrectomy or as soon after as the patient's condition permits.

Stone.—Crane²¹ reported a case in a man in whom a large ureteral calculus formed rapidly. The stone was 4.5 cm. long and formed during a period of seven months. This case illustrates the rapidity with which large calculi may recur in the urinary tract and the futility of treatment unless the source of the trouble is found and removed. Correlating the history, operative data and subsequent course of the patient, it may be assumed that a chronic progressive infection in the kidney was the primary source of the stone.

[COMPILERS' NOTE.—A rapidly growing ureteral stone is of unusual interest. Generally ureteral stones enlarge slowly and may remain the same size for years. Stones in the pelvis of the kidney also develop slowly. Two cases observed over a period of years showed an increase in size of about 20 per cent a year. Rapidly growing stones in the bladder are not infrequently seen; usually they are of the soft, phosphatic type. In a case observed, a stone 5 cm. in diameter developed in a period of five weeks between the two stages of a prostatectomy.]

Squires²² stated that the removal of calculi from the ureter by cystoscopic manipulation or operative cystoscopy has been greatly simplified since this procedure was instituted in 1915. At that time each patient was treated intensively and hospitalized. As a result the reactions and symptoms that occasionally followed cystoscopic manipulation were numerous. The patients are now treated at longer intervals and the catheter is not allowed to remain in the ureter so long; often it is left in place only a few hours, whereas previously it was left in from twenty-four to seventy-two hours. When there is impaction with obstruction and pelvic retention, the catheter is left in place for from twenty-four to seventy-two hours.

The plan of procedure as outlined by Crowell consisted in ureteral dilatation, ureteral anesthesia and lubrication. A 2 per cent solution of procaine hydrochloride is used as an anesthetic; it is allowed to remain in the ureter or renal pelvis for a period of twenty minutes and then is drained; as the ureteral catheter is withdrawn, sterile liquid petrolatum is injected.

In 606 cases of ureteral calculi, 528 calculi were recovered by cystoscopic manipulation and 44 by open operation. In 22 cases the

21. Crane, Whitfield: Rapid Formation of Large Ureteral Calculus with Recurrent Bladder Stone, *J. Urol.* **24**:463 (Nov.) 1930.

22. Squires, C. B.: Disposition of Ureteral Calculi at the Crowell Clinic from 1915 to March 31, 1930, *J. Urol.* **24**:461 (Nov.) 1930.

stone was not recovered. In the majority of cases of cystoscopic manipulation the calculi passed following treatment.

Ureteral Transplantation.—Sisk, Wear and O'Brien²³ reported on thirty-one operations of transplantation of ureters to the sigmoid in 29 dogs. The transplantation was highly unsatisfactory by the Mayo technic. In every case the kidney became infected and closure of the ureterosigmoidal opening by the mucosa of the bowel occurred in five of the seven unilateral transplants. In the 2 cases of bilateral transplants the ureteral openings were markedly stenosed. The Coffey technic gave slightly better results. Complete closure of the ureteral opening occurred in only one ureter. With the unilateral Coffey operation there was no microscopic evidence of pyogenic infection, yet the dogs did not appear to be well after the operation.

Solution of the problem of preventing ascending renal infection probably depends on the discovery of means to prevent infection through the lymphatics. They obtained partial success in this regard in cases in which the exposed end of the ureter was protected for a time from infected material. Until a uniformly successful procedure is evolved, it would seem better to transplant the ureter only in those cases in which older and better understood methods cannot be employed.

Kinks.—Thompson and Bumpus²⁴ called attention to the possibility of producing a kink in the ureter during pyelography when the roentgenogram is made during deep inspiration. They stated the belief that this is the possible explanation of why they were unable to demonstrate such kinks in many cases in which a diagnosis of ureteral kink had been given elsewhere. Three of the cases presented by these authors showed a ureteral kink when the exposure was made during full inspiration and absence of the kink during full expiration.

23. Sisk, I. R.; Wear, J. B., and O'Brien, H. A.: Transplantation of the Ureters to the Sigmoid: An Experimental Study in Dogs, *Surg. Gynec. Obst.* **52**: 212 (Feb.) 1931.

24. Thompson, G. J., and Bumpus, H. C., Jr.: Ureteral Kinks: How They Occur at the Order "Take a Deep Breath and Hold It," *J. A. M. A.* **94**:771 (March 15) 1930.

(To be Continued)

GALLSTONES IN THE COMMON BILE DUCT *

E. STARR JUDD, M.D.

AND

JAMES M. MARSHALL, M.D.

Fellow in Surgery, the Mayo Foundation

ROCHESTER, MINN.

Calculous disease of the biliary system is a condition frequently encountered by the surgeon. Treatment for cholecystitis, with stones, is now a relatively easy surgical problem, and is usually followed by a result that is satisfactory to the patient. However, when the bile ducts become involved either by the passage of stones from the gallbladder into the ducts or by the formation of stones within the ducts themselves, the problem becomes more serious, both for the patient and for the surgeon.

We have recently reviewed a series of 1,608 consecutive cases in which stones of the common bile duct were removed by operation at the Mayo Clinic. This number does not include 160 cases of stones in the ampulla of Vater that we have reported elsewhere. The 1,768 patients who underwent removal of stones from the common bile duct, including the ampulla of Vater, represent 13.2 per cent of all those from whom gallstones were removed during the period corresponding with that during which the cases included in this study were collected. There were 1,120 women and 488 men in this series, a ratio of 2.2 to 1.

The distribution in various groups according to age is interesting. The youngest patient was 5 months, and a fourth of the patients were more than 60 years. It is of interest to note that, on an average, the female patients came for surgical intervention five and a half years earlier than the males.

SYMPTOMS AND DIAGNOSIS

In the diagnosis of stone in the common bile duct, a complete history usually offers the most useful clue, in spite of recent laboratory aids and diagnostic refinements. The most characteristic feature of stone in the common bile duct is the intermittent nature of the symptoms.

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Many years ago, Osler described the typical symptoms of stone in the common bile duct as paroxysms of colicky pain, chills and fever and jaundice, followed by periods of comparative or complete freedom from symptoms. Most patients with stones in the common bile duct present a history of intermittent trouble, although any one or all of the symptoms may be lacking. It is well known that stones in the common bile duct may lie dormant for months or years and apparently cause no symptoms. Sooner or later, however, in most cases there is irritation of the mucous lining of the ducts, which produces an inflammatory reaction with edema around the stone, occluding the duct, and giving rise to biliary obstruction. If infection is present, symptoms of sepsis appear, and if the obstruction is more or less complete, jaundice becomes evident. In most cases these acute symptoms last only a few hours or a few days, and then the attack is over, leaving only residual soreness in the right upper quadrant of the abdomen. But as time goes on the attacks become more and more frequent, with less complete relief in the intervals, so that there is hardly time for recovery from one attack before another one appears.

Pain is the most common and most characteristic symptom of stone in the common bile duct. This usually is of the typical colicky type. In our series of 1,608 patients, 1,293 (80 per cent) had a definite history of one or more attacks of severe, biliary colic which usually required an opiate for relief; 275 (17.1 per cent) complained of pain in the epigastrium, variously called dull, boring or aching, but not sufficiently severe to be classified as colic, and in 40 (2.4 per cent) no pain occurred at any time in the course of the disease.

Jaundice was present in 1,181 (73.4 per cent) of the cases. In 1,105, the jaundice was of the intermittent type, coming in paroxysms, with intervals of complete freedom. In 76, the jaundice was persistent from its onset, but usually varied in degree. Of the 1,181 patients who had jaundice it was present at the time of admission to the clinic in 222 (18.8 per cent). In 427 (26.5 per cent) of the 1,608 cases in the series, the history did not reveal that the patients had been jaundiced at any time.

Symptoms of sepsis with chills and fever were present in 597 (37 per cent) of the cases. These symptoms usually were associated with the attacks of colic and jaundice, but in a few cases recurring chills and fever were the only symptoms present. The chills occasionally were similar to genuine rigor, and were followed by elevation of temperature to 104 or 105 F.

Gastro-intestinal disturbances of one kind or another were reported in most of the cases. Nausea and vomiting occurred in 1,100 (63 per cent), associated with one or more of the attacks. The majority of the

patients complained of chronic dyspepsia, with gas, belching and distress in proportion to the amount of fatty foods and coarse vegetables ingested. This is commonly seen in patients with disease of the gallbladder.

External biliary fistula was present at the time of admission in 39 (2.4 per cent) cases. These occurred in cases in which operation had been performed previously, but in which the obstruction of the common duct had not been relieved.

In the diagnosis of obstructive lesions in the common bile duct, it is important to know whether or not bile is passing from the duct into the duodenum. This can be ascertained easily by passage into the duodenum of a small, soft Rehfuess tube. It has been our experience that when the obstructing lesion is a stone, bile in smaller or larger amounts can be recovered in almost every case, especially if the tube is passed daily for three or four days. This is in contrast to the complete obstructions due to stricture or malignancy of the duct or of the pancreas that sometimes are seen.

Even after a most careful clinical and laboratory study of these cases, the exact diagnosis in a few of them must finally be made on the operating table. This is especially true of the cases of so-called silent stone in the common duct; in these cases, symptoms apparently are absent. The patient with jaundice often presents a difficult problem if one attempts accurately to diagnose the type of lesion which is producing the obstruction, and sometimes the only diagnosis that can be made is of jaundice of the obstructive type. However, if a history is painstakingly obtained, and if the patient is kept for a period of observation in the hospital before operation, surprisingly few mistakes will be made. In the patient who is not jaundiced and in whom the history has been irregular and lacking in one or all of the typical symptoms of stones in the common duct, cholecystography may aid materially in arriving at a diagnosis, especially if the result is positive.

OBSERVATIONS AT OPERATION

In 1,021 (63.5 per cent) of 1,608 cases, stones were found both in the gallbladder and in the common bile duct. In 93 of this group, operations, most of them cholecystostomy, had been performed previously. In 587 (36.5 per cent), stones were found only in the common bile duct. Of the latter group, 149 patients had had the gallbladder removed previously; in the remaining 438, the gallbladder was present but did not contain stones.

We have not attempted to tabulate the number of stones found in the ducts, as in many cases only 1 stone was found, whereas in a few, more than 100 stones were discovered. The common duct that contains

1 stone or more is usually enlarged, and its walls usually are thickened, but sometimes, following cholecystectomy or when the function of the gallbladder has been destroyed by disease, a duct containing no stones may be seen. Frequently when operating, the surgeon is confronted with the problem of whether or not to open the common duct. In many instances, stones cannot be palpated before the duct is opened, especially if they are situated in the lower part of the duct, in the region of the pancreas. It is our practice to explore the duct even when stones cannot be felt, provided that it is unduly enlarged and that there is a definite history of attacks of chills, fever and jaundice. In many instances, on account of a definite clinical history, we have opened the duct and have found stones that could not be palpated before the duct was explored.

The spontaneous formation of a fistula between the gallbladder and an adjacent hollow viscus occurred in 72 patients. In the majority of these, the fistula was between the gallbladder and the duodenum; in a lesser number, the communication was with the colon, and in a few cases, with the stomach.

Pancreatitis was mentioned as an associated lesion in 430 (26 per cent) cases, and marked cholangitis was seen in 67 (4.2 per cent). Varying degrees of hepatitis and biliary cirrhosis were seen in the liver, especially if the condition was of long standing and if jaundice had occurred frequently.

TECHNIC OF OPERATION

Unfortunately, all of the etiologic factors concerned with the formation of gallstones are not known. Neither is the relationship of infection and metabolic disturbances to the formation of gallstones understood. Often it is difficult to tell whether the primary focus of disease is in the gallbladder, bile ducts or liver, or whether the entire biliary system may even be affected. But in the light of present knowledge, surgical intervention offers the only hope of cure for the patient with gallstones.

The first technical point in the operation is to see to it that the incision is sufficiently large to permit the best possible exposure. Exposure of the operative field is more important in this operation than in almost any other. After the incision has been made and the packing off has been completed, the common bile duct should be freed as completely as possible, so that the different technical steps can be carried out without danger of injury to other structures.

When the duct has been exposed, it is usually best to grasp it with two delicate Allison forceps. In certain cases it will be better to use the stone as a guide, holding the stone with the fingers of one hand and making the incision through the duct, down on the stone. The opening in the duct should be large enough, if dilated, to admit the examining finger. A fairly large longitudinal incision in the duct can readily be repaired without any tendency to the formation of stricture. Not infrequently, especially if the duct is large, a scoop or probe will pass by a

stone, thus giving the impression that no stone is present. However, when the duct is large enough to admit a finger, the likelihood of overlooking a stone is reduced considerably.

After the incision has been made in the duct, the bile, *débris* and loose stones should be gently sponged out, and then all the other free stones should be removed as gently as possible from the common and hepatic ducts. We are certain that considerable harm can come from irrigation of the bile ducts if too vigorously applied, although several times we have been able to flush stones out of the ducts of the liver that probably could not have been removed in any other way.

Removal of the stone or stones from the ampulla is best accomplished by first passing a scoop into the ampulla, then guiding the scoop, with the fingers outside the duodenum, gradually manipulating the stone until it is crowded into the hollow of the scoop, and holding it in this position as the scoop is gradually withdrawn. We find that the surest way to palpate a small stone in the ampulla, especially when the surrounding pancreatic tissue is swollen, is to pass a probe, as large as will comfortably fit into the common bile duct, gently down into the ampulla, and then to palpate the ampulla, leaving this instrument in place as a guide. In many cases, the duct is greatly elongated, and there may also be considerable enlargement of the head of the pancreas, which makes it difficult to locate the ampulla even when a stone of fair size is present. A large curved hemostat is one of the best instruments for locating the ampulla and also for demonstrating whether or not it is open. We have frequently been able to pass such an instrument into the duodenum when nothing else would go through the ampulla.

We realize how difficult it is to be sure that all stones have been removed. Occasionally some will be overlooked, even when the greatest care has been exercised, and in some instances stones will form again. We do not feel that efforts to clear out all calculi should be carried to the point of too great trauma to the tissues. We have seen one case of stricture following removal of stone from the ampulla. This, apparently, rarely occurs, but severe infection may follow energetic probing and dilating. If the gallbladder has been removed or destroyed, the activity of the sphincter at the ampulla will be overcome, and there will be a free passage for small stones or *débris* into the duodenum. We believe that it is far more important to provide for prolonged drainage by the insertion of a T-tube, when stone in the common duct occurs, than it is to dilate the passage forcibly into the duodenum. Drainage of the duct should always be carried out after removal of stones, and this is best done with the Deaver T-tube. By this method, complete control of the flow of bile is obtained after the wound has healed around the tube. If the lower end of the duct is opened widely, bile will pass through the tube into the duodenum; whereas if the ampulla is closed because of swelling or another cause, the bile escapes to the outside through the long arm of the tube. When bile is needed for the welfare of the patient, it may often be forced into the duodenum by clamping the outside tube. Another advantage of this plan of

drainage is that this tube may be used as MacArthur suggests, that is, for the administration of fluids, dextrose and any form of liquid nourishment.

It is our practice to remove the gallbladder in all cases of stone of the common duct when jaundice is not present or when the operative risk is not materially increased. When the patient is deeply jaundiced, we feel that the additional operation involved in removal of the gallbladder with exposure of the surface of the liver is not justified, except in an occasional instance. In most of these cases cholecystostomy is done, with removal of the stones, in addition to choledochostomy.

POSTOPERATIVE TREATMENT

The intravenous administration of a 10 per cent solution of dextrose has proved to be a great help in treating patients after operation; this is especially so if the patients are jaundiced or if the liver has been considerably injured by the disease. We give 1 or 2 liters as a routine injection each day for the first few days after operation. As soon as the patient is able to take nourishment, carbohydrates are given freely, and often 30 cc. of karo corn syrup twice daily is prescribed as an aid to recovery of hepatic function.

In the average cases of stone in the common bile duct, the drainage of bile to the outside through the T-tube will begin to diminish after the first week. At the end of the second week considerable bile is usually entering the duodenum, and at this stage we begin to clamp the long arm of the T-tube for a few minutes each day. The time during which the tube is clamped is gradually increased, and usually by the end of the fourth week the tube can be clamped all of the time with perfect comfort to the patient. By this time the stools are well colored with bile, and then the T-tube is removed.

If the patient is deeply jaundiced at the time of the operation, or if marked cholangitis and hepatitis are present, prolonged drainage is indicated. In such cases, we frequently leave the tube in place for several months, and occasionally for a year.

The most frequent postoperative complications are peritonitis, pneumonia, hemorrhage and hepatic and renal insufficiency. Many patients constitute poor risks from a surgical standpoint on account of age, jaundice and hepatic disease of long standing; it is in this group that most of the deaths occur. In patients who seek relief early in the course of their illness, before their general health has become materially impaired, and before the liver has become extensively diseased, operation can be done with a risk that is very little greater than that encountered in cholecystectomy. In the patient with jaundice, the

tendency to hemorrhage after operation is present, and we feel that small transfusions of whole blood are of definite benefit in controlling the bleeding.

RESULTS

In the series of 1,608 patients, the mortality rate was 6.7 per cent. Various causes were responsible for the number of deaths represented by this percentage, as follows: local or generalized peritonitis, 24 per cent; pneumonia, 24 per cent; hemorrhage in one form or another, 18 per cent; acute or chronic nephritis with renal insufficiency, 10 per cent, and pulmonary embolism, 7 per cent. The remainder of the deaths were due to cardiac failure, suppurative cholangitis, diabetes mellitus, meningitis, ulcerative colitis and atrophy of the liver with hepatic insufficiency.

The patients who survived the operation were, in the great majority of cases, completely relieved from their symptoms and have remained well. In the follow-up records it is found that 75 (4 per cent) have returned to the clinic because of recurring trouble, and in 55 of these, stones were again removed from the common bile duct.

ANEURYSM OF THE SPLENIC ARTERY

REPORT OF A CASE AND REVIEW OF THE LITERATURE *

WILLIAM E. LOWER, M.D.

AND

JAMES I. FARRELL, M.D.

CLEVELAND

The occurrence of aneurysms of the abdominal vessels is considered unusual, but as the result of improvement in diagnostic technic, aneurysms have come to occupy an important position among the lesions of the abdomen of which there are no pathognomonic signs. Of this group, splenic aneurysms are perhaps the most uncommon, since Anderson and Gray,¹ who recently published an admirable summary of the subject, were able to collect only 58 clinical cases. In but one of these was the lesion diagnosed preoperatively. Schroeder,² who made a study of splenic aneurysms, collected statistics from the larger pathologic museums of Europe, and in his series of 32,768 autopsies, only 20 cases of splenic aneurysm are included. Of the clinical cases reported, operation was performed in 15. The diagnosis was made preoperatively only once, by Högler,³ from the following symptoms and signs: sudden attacks of pain in the upper left quadrant of the abdomen, a filling defect in the stomach along the lesser curvature and a systolic blow over a palpable tumor.

Winckler⁴ performed an operation for a splenic aneurysm in which he removed the spleen also. His patient recovered, and lived for twenty-five years. In his paper he considered the advisability of splenectomy in the presence of splenic aneurysm, stating that he felt it to be a hazardous procedure.

Villard and Murard⁵ gave an account of a case in which operation was performed for a pancreatic cyst, but an aneurysm of the splenic

* Submitted for publication, Dec. 6, 1930.

* From the Cleveland Clinic.

1. Anderson, W., and Gray, J.: Report of a Case of Aneurysm of the Splenic Artery, with References to 58 Cases Collected by Authors, *Brit. J. Surg.* **17**:267, 1929.

2. Schroeder, Carl: Ueber einem Fall von Aneurysma der Arteria lienalis, *Arch. f. klin. Chir.* **132**:175, 1924.

3. Högler, F.: Beitrag zur Klinik des Leber- und Milzarterienaneurysmas, *Wien. Arch. f. inn. Med.* **1**:543, 1920.

4. Winckler, V.: Ein Fall von Milzexstirpation wegen Aneurysma der Arteria lienalis, *Zentralbl. f. Chir.* **32**:257, 1905.

5. Villard, E., and Murard, J.: Anévrisme de l'artère splénique, *Arch. gén. de chir.* **8**:749, 1912.

artery was found. They used a tampon instead of attempting to remove the tumor, and the patient died twelve days later.

In Mulley's ⁶ case, a diagnosis of left hydronephrosis was made. At operation, a large solid tumor was found near the splenic vessels which, on inspection, proved to be an aneurysm. The spleen was removed along with the tumor, and the patient recovered.

Garland ⁷ described a case in which rupture of a splenic aneurysm was caused by an abdominal paracentesis, which caused the patient's death.

Smith ⁸ gave the history of a Negress who was brought into a hospital in shock. A diagnosis of ectopic pregnancy was made. At operation much blood was found in the lesser omental sac, and further examination revealed a splenic aneurysm which had ruptured. The bleeding was controlled with tampons, but the patient died two hours later. In this case the aneurysm had pressed on the pancreas and had caused atrophy.

Lundwall and Gödl ⁹ described an aneurysm of the splenic artery which ruptured during the ninth month of pregnancy, causing the death of the patient. A supravaginal hysterectomy was done in an attempt to prevent bleeding, the source of which was in the abdominal cavity. Only at autopsy, however, was the lesion of the splenic vessel found.

In Schroeder's ² case, there was a swelling on the left side, with blood in the stools. At operation he found a cirroid aneurysm of the splenic artery, with an enlarged spleen weighing 3,000 Gm. The patient died after the operation.

Fitzwilliams ¹⁰ performed an exploratory laparotomy for shock combined with abdominal pain. He found a ruptured aneurysm of the splenic artery. The patient died within four hours.

Davis ¹¹ operated because of a tumor which appeared just to the left of the umbilicus. He succeeded in removing the mass, and the patient made an uneventful recovery.

6. Mulley, K.: Ein Fall von Aneurysma der Arteria lienalis, geheilt durch Splenektomie, Beitr. z. klin. Chir. **111**:205, 1918.

7. Garland, J.: Aneurysm of the Splenic Artery, Rupturing Simultaneously with Paracentesis Abdominis, Boston M. & S. J. **184**:385, 1921.

8. Smith, W. R.: A Case of Ruptured Aneurysm of the Splenic Artery. J. A. M. A. **80**:1692 (June 9) 1923.

9. Lundwall, K., and Gödl, A.: Aneurysm of the Splenic Artery, Arch. f. Gynäk. **118**:177, 1923.

10. Fitzwilliams, D. C. L.: Fatal Case of Aneurysm of the Splenic Artery. Brit. M. J. **2**:803, 1924.

11. Davis, B. F.: Aneurysm of the Splenic Artery: Operative Removal. J. A. M. A. **84**:200 (Jan. 17) 1925.

Näher¹² removed a splenic aneurysm together with the spleen, and his patient was cured.

Saenger¹³ gave the history of a patient who suffered from sudden pain in the abdomen followed by collapse. An operation was performed and an eight months' fetus was found. Free blood in the peritoneal cavity led to the discovery of an aneurysm of the splenic vessels.

Goullioud¹⁴ operated in a case in which he found an aneurysm of the splenic artery. He was unable to dissect the mass free, and therefore tied the large vessels entering and leaving it. The patient made an uneventful recovery.

Faehrmann and Ugrümow¹⁵ operated on a man suffering from paroxysmal pain, and found an enlarged spleen with hemorrhagic ascites, together with a bleeding point in the splenic artery. Tampons were used, but the patient died twelve hours later. Autopsy revealed an aneurysm of the splenic vessels.

Marshall¹⁶ performed an operation on a patient who had a wound from a gunshot in the abdomen, and found a pancreatic fistula, which finally closed. Five months later, the patient was readmitted with an aneurysm of the splenic artery. A gauze pack was used to control bleeding, and a pancreatic fistula was again formed.

The following case is presented because of the patient's long illness, the unusual pathologic condition which was found and the favorable outcome of surgical intervention:

REPORT OF CASE

History.—A boy, aged 16 years, was admitted to the Cleveland Clinic on March 15, 1930, complaining of attacks of severe abdominal pain. The mother gave the following history. Shortly after recovery from an attack of whooping cough, which had occurred eight years previously, paroxysms of pain had suddenly developed in the pit of the stomach. These were so intense that the patient would writhe on the floor and apply pressure to his abdomen in an effort to secure relief. The pain was not related to meals, but came on at any time. During the preceding six months, it had occurred more frequently, and at the time of this consultation the patient had as many as two or three attacks a day. Morphine in one-half grain (0.32 mg.) doses afforded some relief. After an attack of pain the stools were tarry, and on examination they were found to contain much blood.

12. Näher, H.: Aneurysms of Splenic Artery, *Deutsche Ztschr. f. Chir.* **198**: 118, 1926.

13. Saenger, Hans: Fatal Hemorrhage in Eighth Month of Pregnancy from Rupture of Aneurysm of Splenic Artery, *Zentralbl. f. Gynäk.* **50**:1324, 1926.

14. Goullioud, M.: Aneurysm of the Splenic Artery with Surgical Ablation, *Lyon méd.* **142**:353, 1928.

15. Faehrmann, I., and Ugrümow, B.: Aneurysm in Splenic Artery, *Arch. f. klin. Chir.* **137**:193, 1925.

16. Marshall, C. J.: Traumatic Aneurysm of the Splenic Artery with Rupture and Ligature, *Brit. J. Surg.* **9**:570, 1922.

The patient had had the usual diseases of childhood. His tonsils were removed when he was 7 years of age, and a biopsy had been done on a gland in the neck in an attempt to rule out Hodgkin's disease. There was no history of respiratory, cardiac or renal trouble. The family history was unimportant.

Examination.—Physical examination revealed a slim, pale, undernourished boy about 50 pounds (22.71 Kg.) underweight for his height. The temperature was 99.4 F., the pulse rate 128 and the blood pressure 100 systolic and 60 diastolic. The skin was a pale yellow, and the mucous membranes were pallid. The head and neck were essentially normal. On examination of the chest, some râles were heard in the upper lobe of the left lung. The heart was normal in size, shape and position, but there was a slight systolic murmur at the apex which was thought to be functional. The abdomen was slightly distended, but no fluid, scars or masses could be detected. The remainder of the physical examination revealed nothing of significance.

Examination of the blood gave the following results: red blood cells, 1,700,000; white blood cells, 4,600, and hemoglobin, 40 per cent. The differential count was: polymorphonuclear cells, 61 per cent; lymphocytes, 39 per cent, and transitional cells, 1 per cent. The red cells showed central pallor and a marked variation in size and shape.

Urinalysis gave negative results.

The chemical analysis of the blood showed the sugar, urea, uric acid, calcium, phosphorus, cholesterol and serum bilirubin to be within normal limits. The Wassermann and Kahn tests of the blood were negative.

Examination of the stool revealed much occult blood but no parasites, and a culture from the stool showed colon bacilli and gram-positive diplococci.

A roentgenogram of the chest indicated that there was considerable fibrosis of the hilus and of the upper lobe of the left lung. A roentgenogram of the abdomen suggested nothing abnormal. A roentgenographic study of the gastro-intestinal tract revealed a functioning gallbladder, a normal stomach, deformity and hypermotility of the duodenum and a smooth and hypermotile colon.

From these observations, a tentative diagnosis of chronic pancreatitis was made. Other possibilities considered were diaphragmatic hernia, Meckel's diverticulum and congenital adhesions.

The patient was admitted to the hospital and given a transfusion of 500 cc. of whole blood. He was given a high caloric diet and was placed at rest in bed. The pain continued, and there were no signs of improvement. To ascertain the underlying pathologic process, an exploratory laparotomy was decided on.

Operation and Course.—With the patient under spinal anesthesia, a high left rectus incision was made, extending from the xiphoid process to the umbilicus. No gross pathologic process was found in the stomach. The duodenum apparently was dilated and hypertrophied. No scarring was present in the duodenal wall. Examination of the large bowel disclosed no gross abnormalities. Inspection of the jejunum revealed a tumor just above and to the left of the ligament of Treitz. This tumor was firmly adherent to the intestinal wall and was bound down to the vessels leading to the hilus of the spleen. Palpation showed this mass to be solid and apparently attached to the pancreas. A needle was inserted into the tumor in an effort to ascertain its contents, but nothing could be aspirated. The operator then began to dissect the mass free from the intestine, which proved to be easy. While attempting to liberate the mass from the splenic vessels, hemorrhage occurred, and a transfusion was performed during the operation. Hemostasis was secured with forceps and ligatures. The mass could not be dissected free from the pancreas, and the tail of the pancreas, therefore, was removed with

the tumor. The pancreatic duct was found to be markedly dilated, which in all probability was due to pressure on the pancreas. The operator decided that it would be best to bring the cut end of the pancreatic duct up to the abdominal incision, so that if leakage occurred it would drain to the outside. The abdomen was closed without a drain.

After the operation the patient had a rather high temperature, which gradually subsided and became normal at the end of the sixth day. About the seventh day the pancreatic duct that had been sewed into the abdominal wound showed some tendency to discharge. With cauterization by means of silver nitrate, however, this duct healed satisfactorily.

The patient was seen two months after the operation, and he reported that there had been no recurrence of the pain. He had gained 25 pounds (11.3 Kg.)

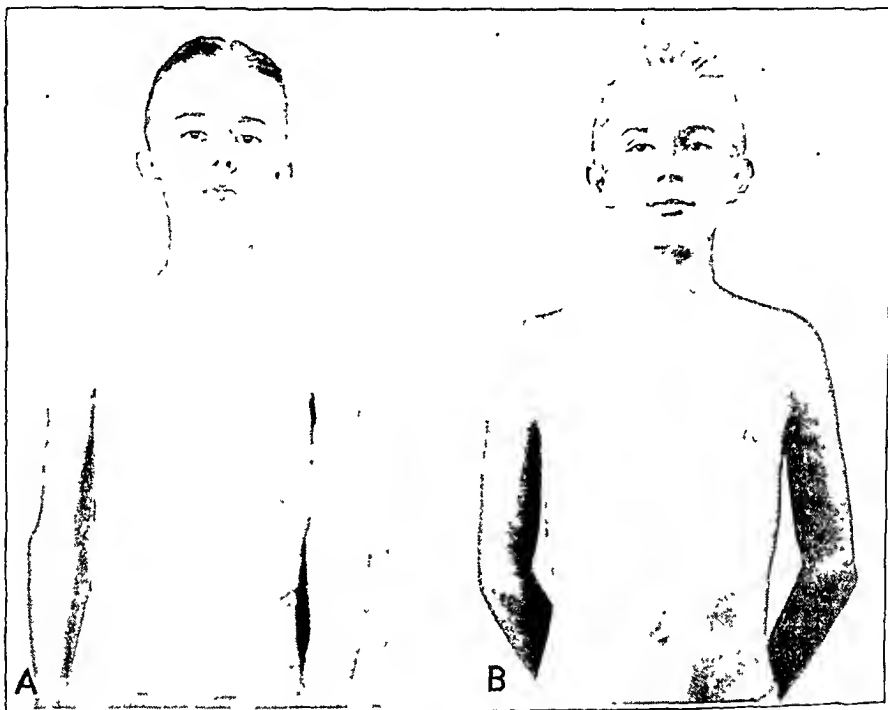


Fig. 1.—*A*, patient two weeks after operation for aneurysm of the splenic artery; *B*, six months after operation. Note the improved state of nutrition.

in weight, and his appetite was much increased. The anemia had progressively lessened until, at the time of this examination, the hemoglobin was 80 per cent and the red cell count 4,500,000.

The patient's gain in weight following operation was slow despite his good appetite. In view of the fact that about a third of the pancreas had been removed, an examination of the feces was made. The stool was very bulky, and contained much undigested material. The normal stool contains from 30,000 to 60,000 units of amylase. (By a unit of amylase is meant the number of cubic centimeters of 1 per cent solution of starch which would be digested by 3,000 cc. of fecal suspension in one-half hour at a temperature of 38 C.) The patient's stool contained less than 3,000 units, and the trypsin content was likewise very low. A fecal suspension of 1.8 cc. failed to digest 5 cc. of a 1 per cent solution of casein.

The stool, stained with sudan III, showed many crystals of fatty acid, and fat globules were present. In order to augment pancreatic digestion, pancreatin,

a dried gland preparation, was given in doses of 10 grains (0.65 Gm.). Following a period of treatment with pancreatin, the patient began to gain weight. While the pancreatin was being administered, the stool was again examined and found to contain the pancreatic enzymes within normal limits. Because of the deficiency in external pancreatic secretion, the blood sugar content and the dextrose tolerance curves were examined, but the patient did not show any evidence of hyperglycemia.

Pathologic Report.—The pathologic report was as follows: The specimen (fig. 2) consisted of a portion of the tail of the pancreas and an attached aneurysmal sac, weighing 40 Gm. The portion of the pancreas, apparently the tail end, measured 5 cm. in length, 2.5 cm. in width and 1 cm. in thickness. It was covered by fibrofatty tissue, and there were numerous lymph nodes in this tissue on the posterior surface of the pancreas. There was a central ductlike structure running longitudinally through the pancreas. This channel was dilated, irregular and surrounded by fibrofatty and pancreatic tissue. Attached to the anterior surface



Fig. 2.—Gross view of specimen of aneurysm of the splenic artery. The threads show the course of the blood vessels through the aneurysm. The vertical thread is passed through the splenic artery, while the horizontal thread runs through a branch of the splenic artery and the aneurysmal sac.

of the pancreas there was a large, round, encapsulated mass which had been ruptured. It consisted of a sac, apparently the wall of a blood vessel, and except for an irregular cavity near the center it was filled with a laminated blood clot. At the posterior extremity there was an opening about 2 mm. in diameter, apparently a blood vessel. Along the superior border and parallel to the pancreas there was a segment of a vein and of an artery, the splenic vessels. From about the middle point of the arterial segment, a branch led into the aneurysmal sac.

On microscopic examination, pancreatic tissue was seen, with extensive fibrosis and loss of glandular tissue. Some of the lobules were represented only by small and by large ducts. There were numerous large masses of islet tissue, which histologically were normal. Neither active acute inflammation nor acute necrosis was seen. Sections from the wall of the aneurysm showed a fibromuscular coat externally and a thick layer of organized and recent blood clot internally.

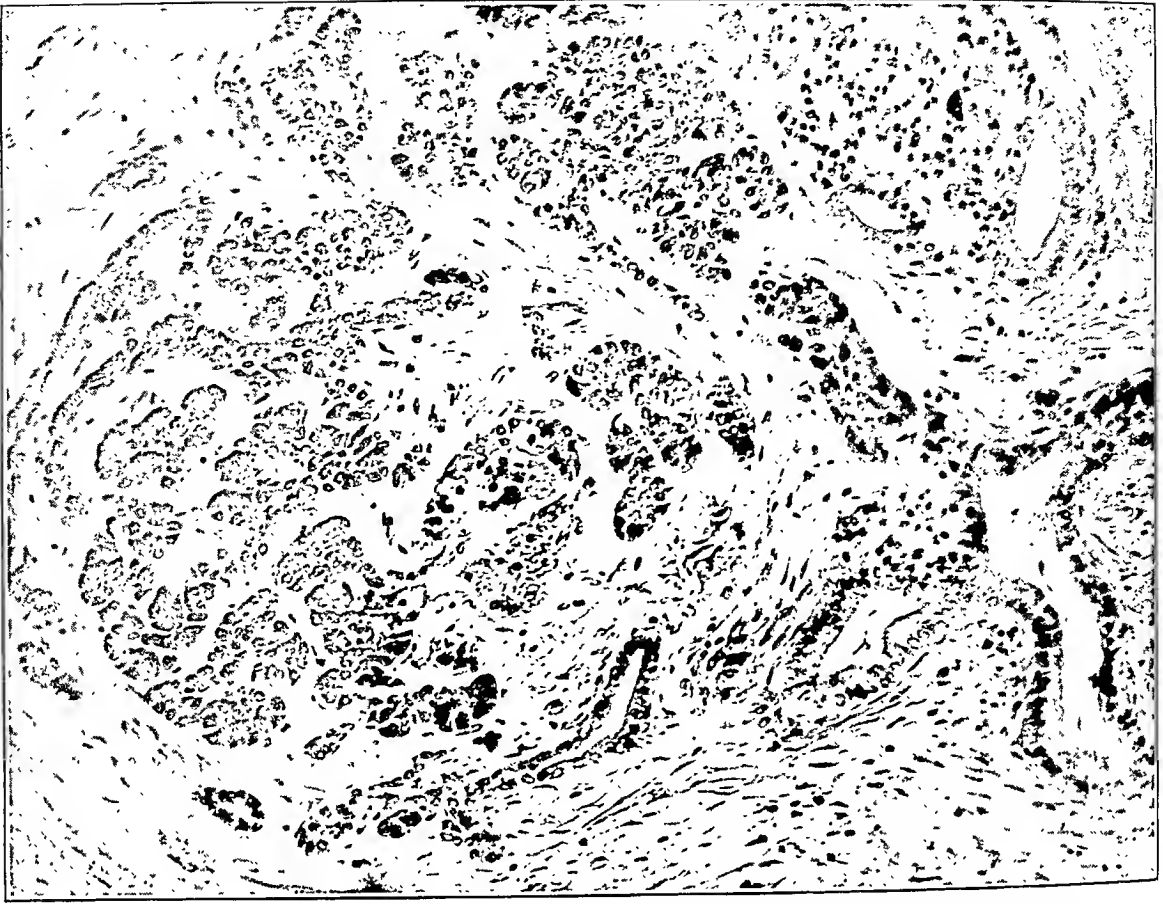


Fig. 3.—Photomicrograph showing atrophy and fibrosis of the pancreatic glandular tissue; $\times 150$.

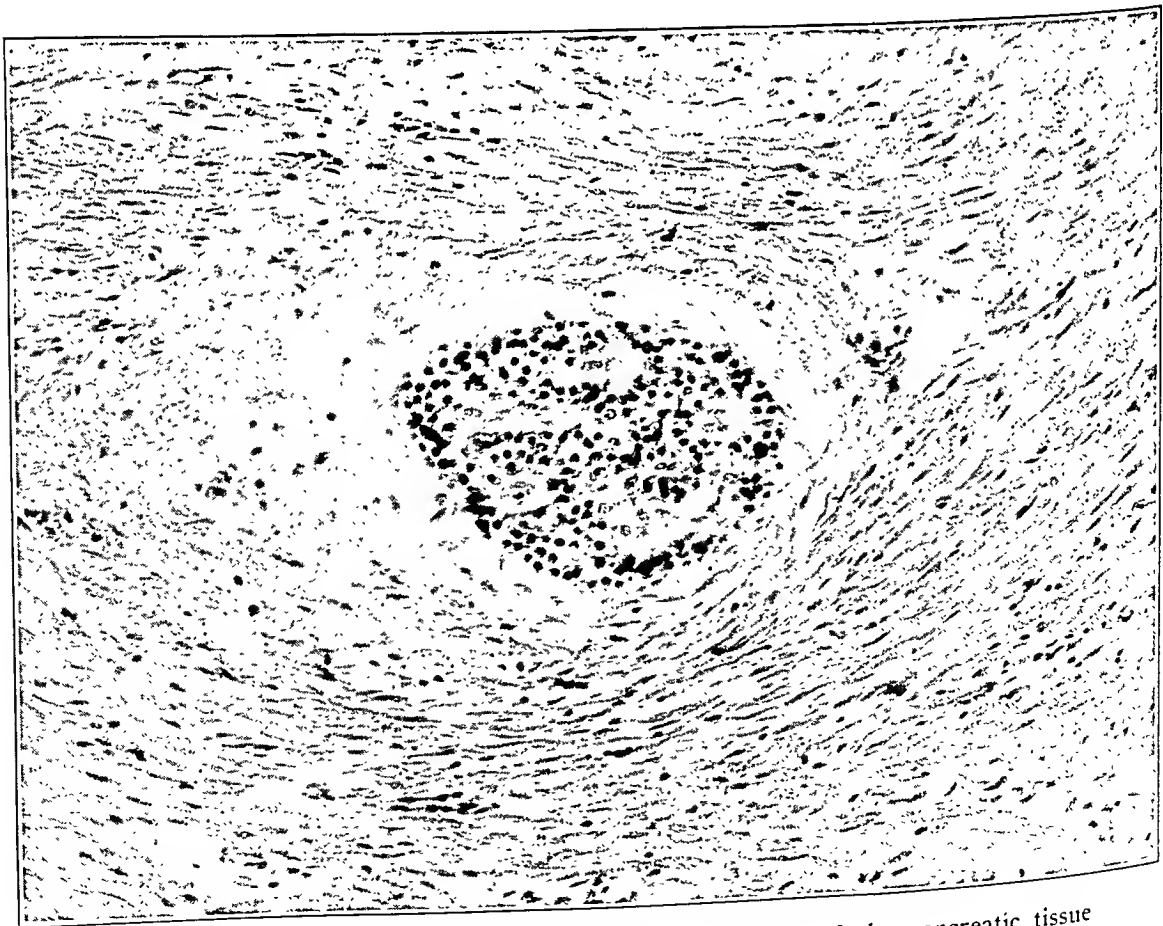


Fig. 4.—Photomicrograph showing complete atrophy of the pancreatic tissue and persistence of the islet tissue; $\times 150$.

COMMENT

The absence of any constant pathognomonic symptom or sign of splenic aneurysm is striking. The two most common observations in cases of aneurysm of the splenic vessels are unheralded paroxysmal attacks of pain in the left side of the epigastrium and tarry stools. The pain is much more severe than that due to organic lesions in the stomach, and should not be mistaken for the pain caused by a gastric ulcer. In addition, there is considerable anemia, and not infrequently there is a pancreatic deficiency which may be detected by examination of the stool for undigested fat. The roentgenologic examination usually does not show anything definite, although in Höglér's case,³ in which the aneurysm was large, the pulsations could be seen under the fluoroscope when a barium meal was given. One feature of the abdominal examination which is usually omitted is auscultation. In only one case was a definite bruit heard over the vessel.

The case report presented here demonstrates that a pancreatic deficiency may accompany a splenic aneurysm. The type of deficiency involves only the glandular tissue concerned with external secretion. The islet tissue remains intact. This observation has been made repeatedly in experimental animals in which the pancreatic duct has been ligated. It is noteworthy that the pancreatin given by mouth corrects the deficiency in pancreatic digestion.

Fifteen cases of splenic aneurysm for which operation has been performed are reported in the literature. In this series, seven patients have recovered from the operation and eight have died, many of the latter having entered the hospital in a state of shock or collapse. In four cases a tampon was used to control bleeding, and in every instance the patient died. In two of the cases in which recovery followed operation, the spleen was removed, and in one, the vessels leaving and entering the aneurysm were tied. In Smith's case⁸ the tail of the pancreas was involved, causing atrophy by pressure. In the authors' case also, the tail of the pancreas was involved, with atrophy of the parenchyma and a dilatation of the pancreatic duct.

From a study of the reports of operations performed for splenic aneurysm, it appears that the most important detail is to secure hemostasis, as ligation of the vessels or splenectomy was usually followed by recovery. In all the cases in which a tampon was used to control bleeding, the patients died. The vessels affected can be ligated without serious results. When the splenic artery is involved, ligature of the vessel causes an aseptic atrophy of the spleen, which should cause no mortality, as this has been done many times in experimental animals, and several times in human subjects without any serious effects.

CONCLUSIONS

In cases exhibiting paroxysmal attacks of pain in the upper portion of the abdomen accompanied by gastro-intestinal hemorrhages and an epigastric tumor, and in which roentgenologic examination fails to disclose an organic lesion of the stomach, the possibility of a splenic aneurysm should be considered. In view of the pancreatic involvement in two cases of splenic aneurysm, an examination of the stools for undigested fat should be made in order to determine whether or not a pancreatic deficiency exists. A study of the enzymatic strength of the urine also would be useful, since in diseases of the pancreas an increased amylase content is not infrequently found in the urine. In all cases of abdominal tumor, stethoscopic examination should be made as a routine measure in order to determine the presence or absence of a bruit.

In operating on an aneurysm of the abdominal cavity, accurate hemostasis is essential, as in all cases in which a tampon was used, the patients died. If removal of the spleen is necessary for hemostasis, or ligation of the splenic artery and vein is essential, either may be done without fatal results.

NORMAL THYROID IN RELATION TO THE CLASSIFICATION OF GOITERS

HISTOLOGIC STUDIES *

J. WILLIAM HINTON, M.D.

Assistant Professor of Surgery, New York Post-Graduate Medical School and
Hospital; Assistant Attending Surgeon, Bellevue Hospital

NEW YORK

After examining patients with thyroid diseases, one is chiefly concerned as to the method of treatment indicated to restore these persons to normal with the shortest period of disability. From writings on both the clinical and the pathologic aspects of thyroid diseases, one is led to believe that there are different types of goiter which remain constant, and that the treatment can be outlined according to the type. Whether goiters of different types do represent definite clinical entities has not been settled, but Hertzler¹ was the first to point out that they may represent merely stages of a continuous disease.

In view of the fact that there is a difference of opinion as to whether one is dealing with a continuous process or different diseases, it was thought advisable to undertake a study of the normal thyroid to determine whether there is a relatively constant histologic picture for the different periods of life from the fetal to the senile stage. In a recent paper² a report was made on the study of sections from 107 cases. It was my purpose to obtain sections from a large series of cases in which death was accidental, rather than serial sections from a few cases, as the study of a large group would represent more nearly the pathologic reports on operative specimens. Of 80 cases in which death was accidental the age varied from stillbirth to 89 years. I was unable to find a relatively constant histologic picture for different ages, and the sections were so variable that it was difficult to conclude what was normal. There were also 16 cases in which death resulted from acute diseases and 11 in which it resulted from chronic diseases, but the sections failed to reveal any definite changes.

Figures 1 to 7 inclusive illustrate how variable the histologic changes are in people of apparently normal health. In a specimen

* Submitted for publication, Oct. 20, 1930.

* Read before the Yorkville Medical Society, Oct. 20, 1930.

1. Hertzler, Arthur E.: Pathogenesis of Goiter Considered as One Continuous Disease Process, *Arch. Surg.* **16**:61 (Jan.) 1928.

2. Hinton, J. William: Histologic Studies of the Thyroid Gland, *Am. J. Surg.* **11**:269 (Feb.) 1931.

obtained from a female infant; stillborn due to cranial injuries, the epithelial cells were closely spaced with the gland divided into lobules by connective tissue with the absence of acini (fig. 1). In a boy, aged 10 weeks, who died of pneumonia, the acini were well formed with an abundance of both interacinal and interlobular connective tissue (fig. 2). This is contrary to Hertzler's³ opinion that the connective tissue is more abundant in elderly people. A boy, aged 13 years, who died from

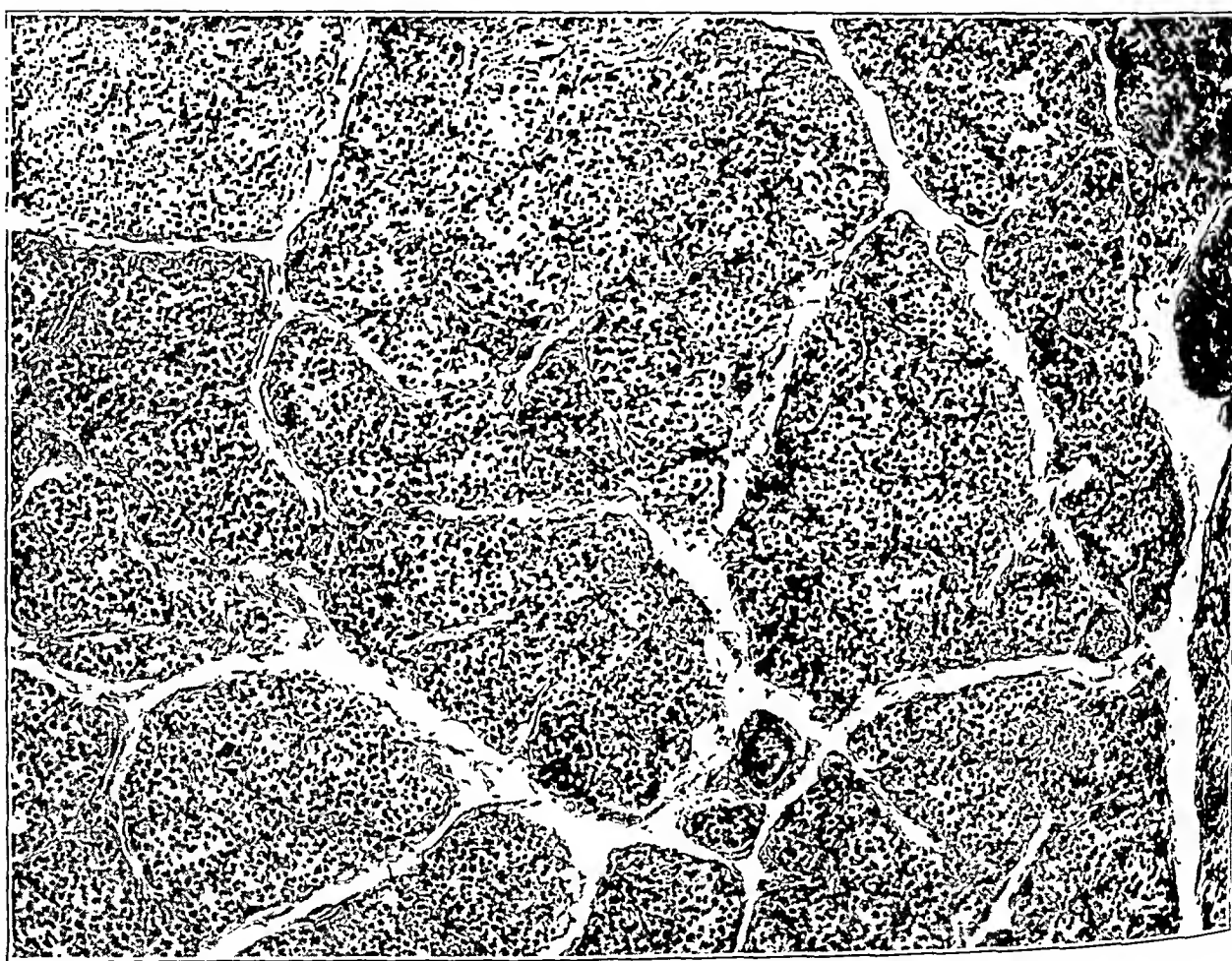


Fig. 1.—Section from a female infant, stillborn, due to cranial injuries.

a fractured skull, showed large acini which contained colloid (fig. 3). In a man, aged 25, who was shot by the police and instantly killed, the acini were very large, contained colloid, and were lined by flat epithelium (fig. 4). In a woman, aged 35, who died from a fractured skull, the gland was divided into lobules by connective tissue but made up chiefly of undifferentiated epithelial cells. A woman, aged 61, committed suicide by strangulation. In the specimen obtained in this case, the

3. Hertzler, Arthur E.: *Diseases of the Thyroid Gland*, ed. 2, St. Louis, C. V. Mosby Company, 1929.

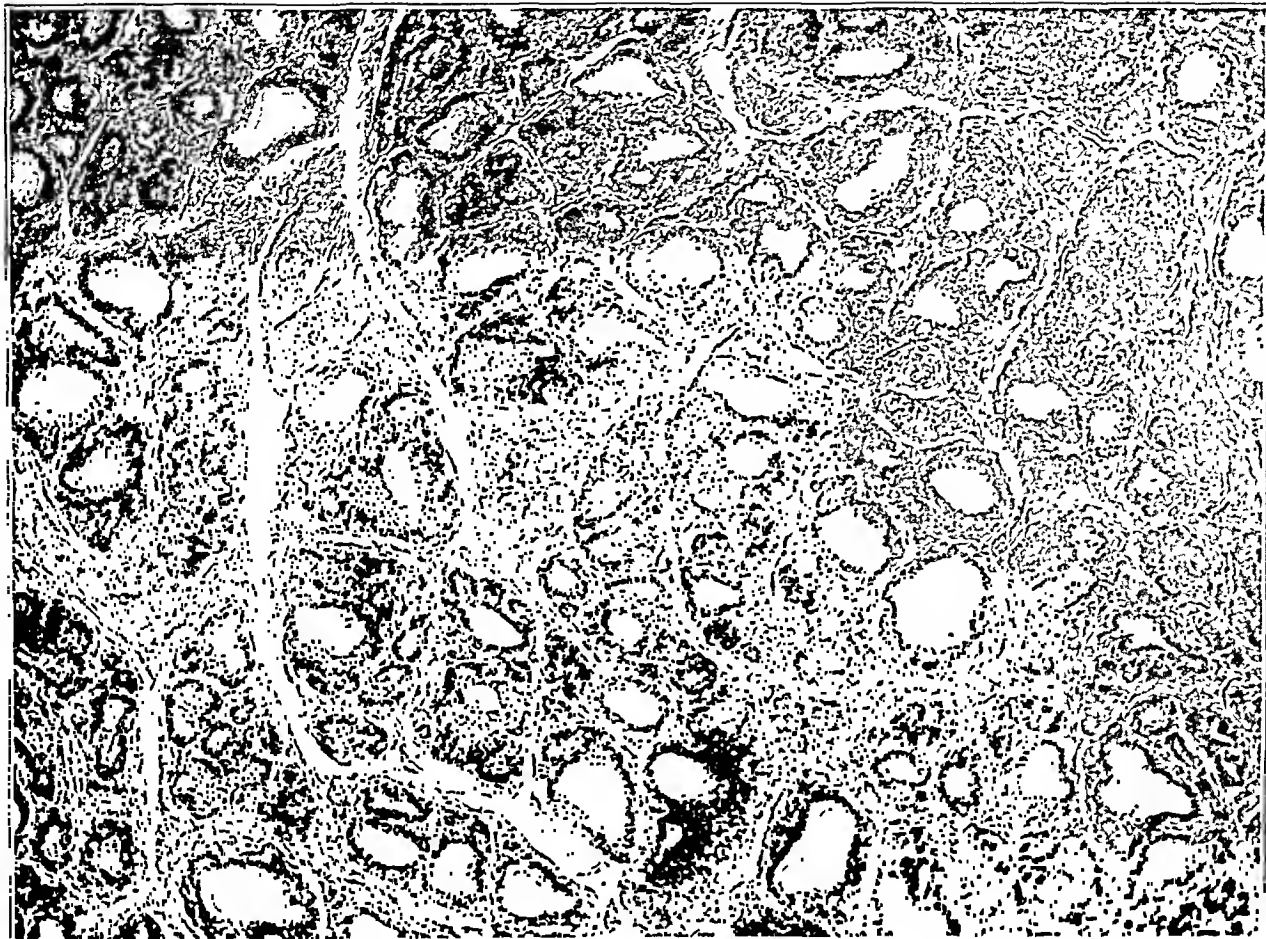


Fig. 2.—Section from a boy, aged 10 weeks, who died of pneumonia.

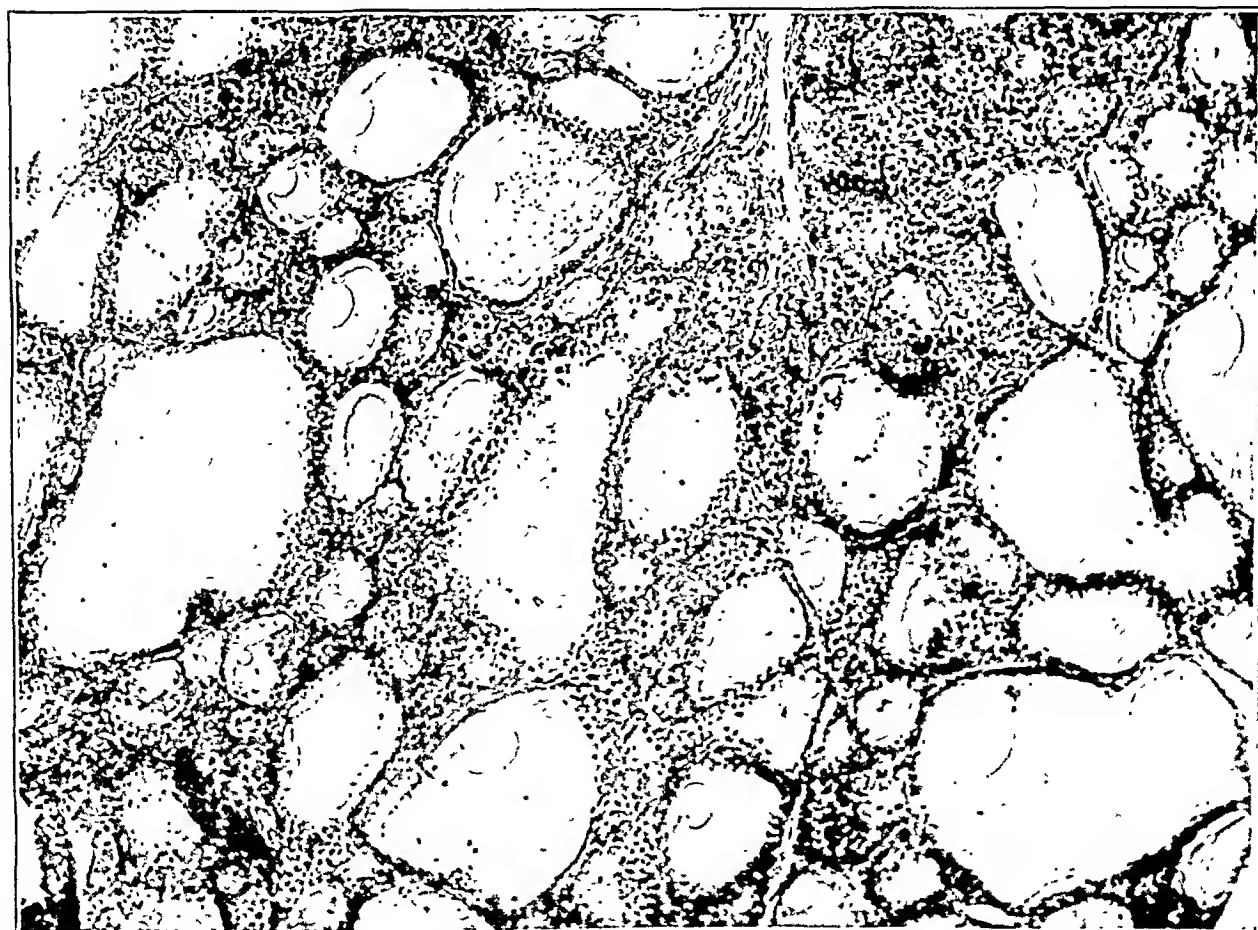


Fig. 3.—Section from a boy, aged 13 years, who died from a fractured skull.

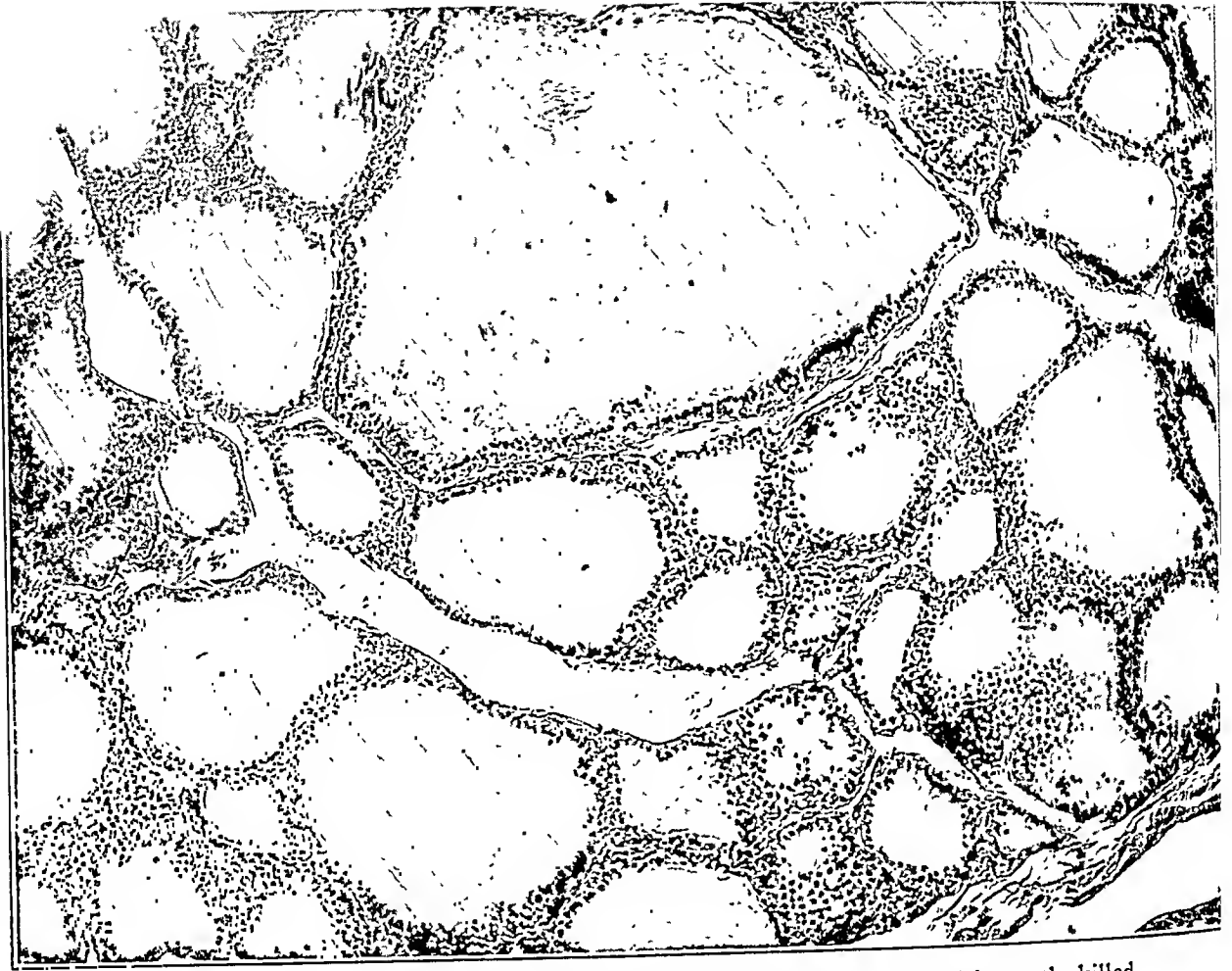
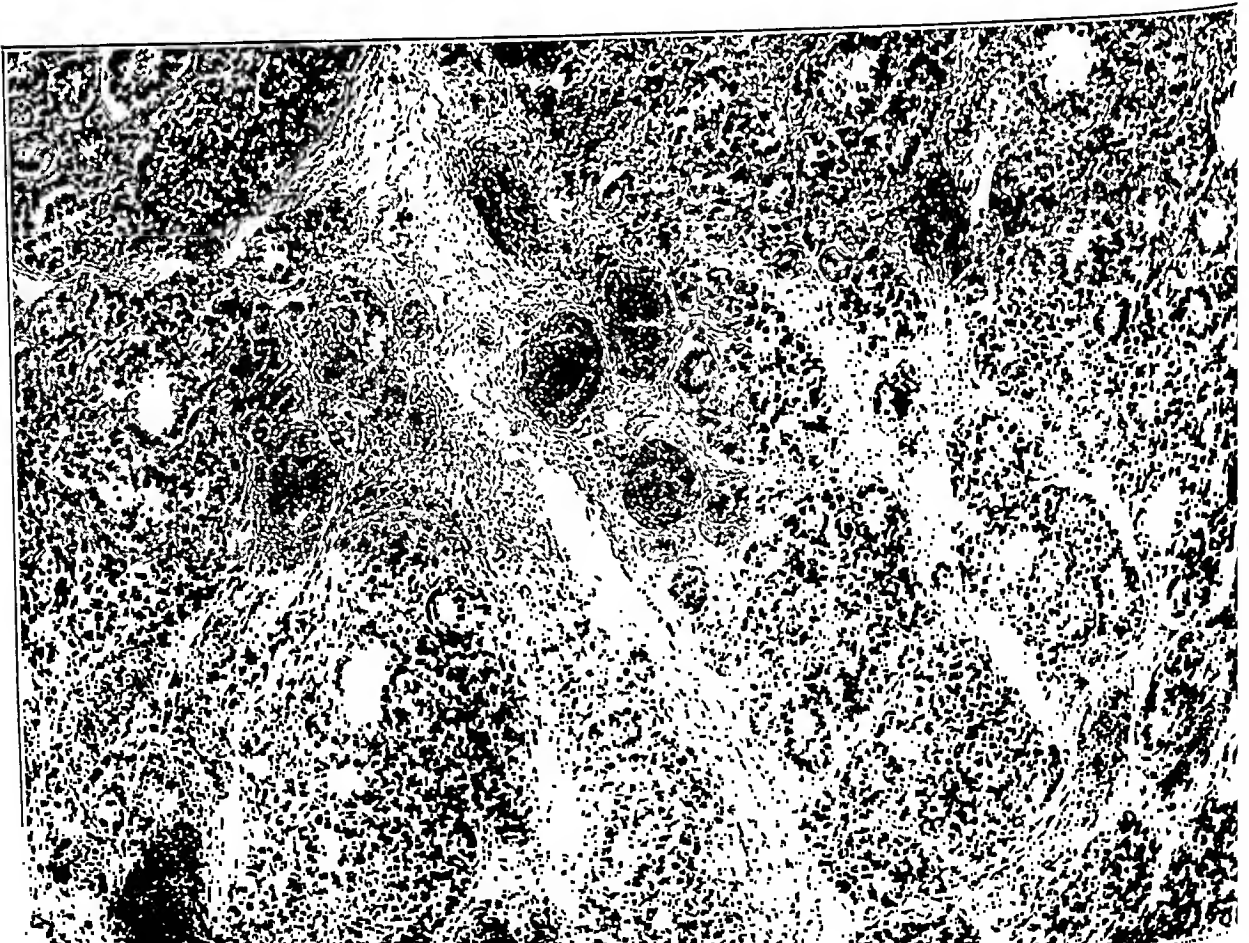


Fig. 4.—Section from a man, aged 25, who was shot by the police and instantly killed.



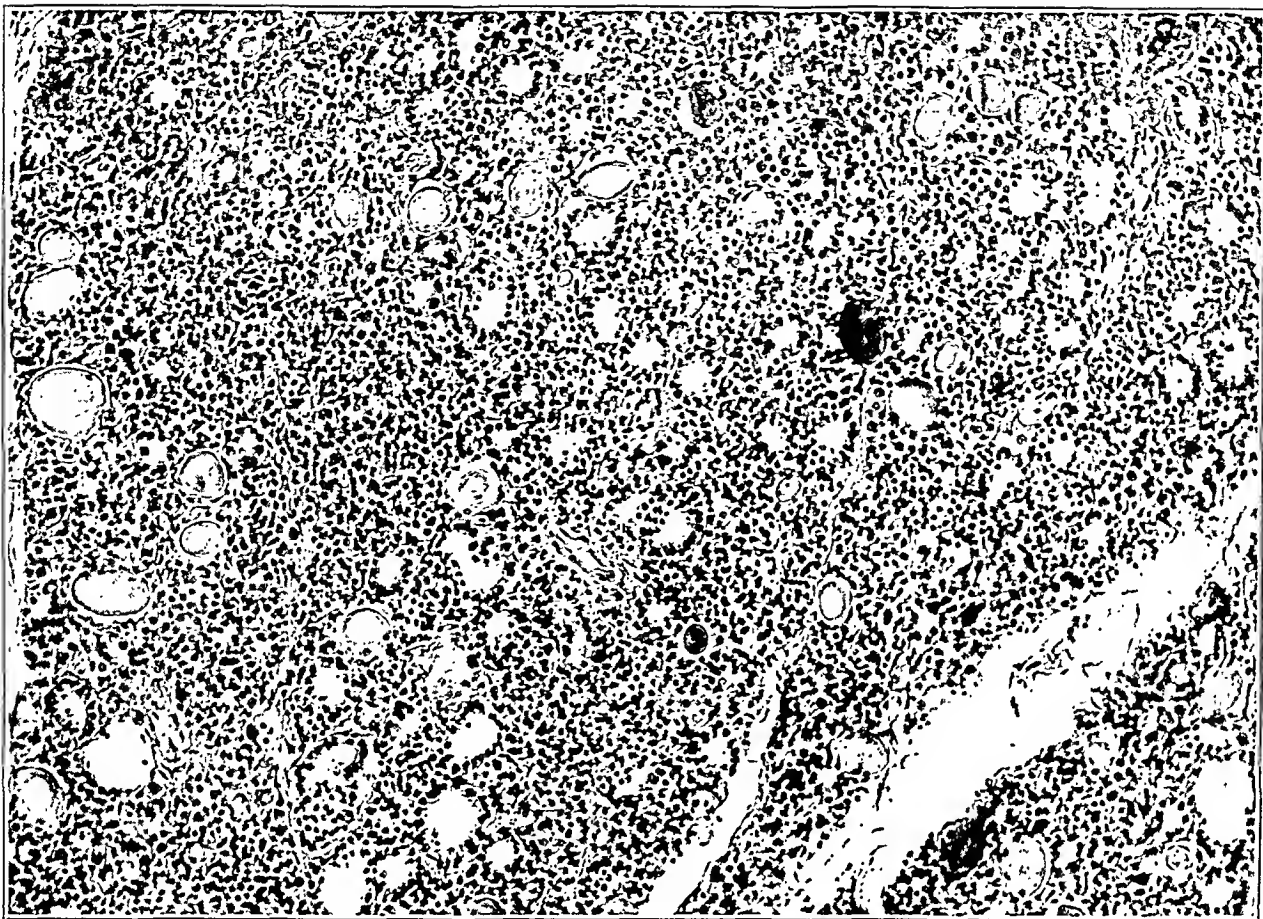


Fig. 6.—Section from a woman, aged 61, who committed suicide by strangulation.

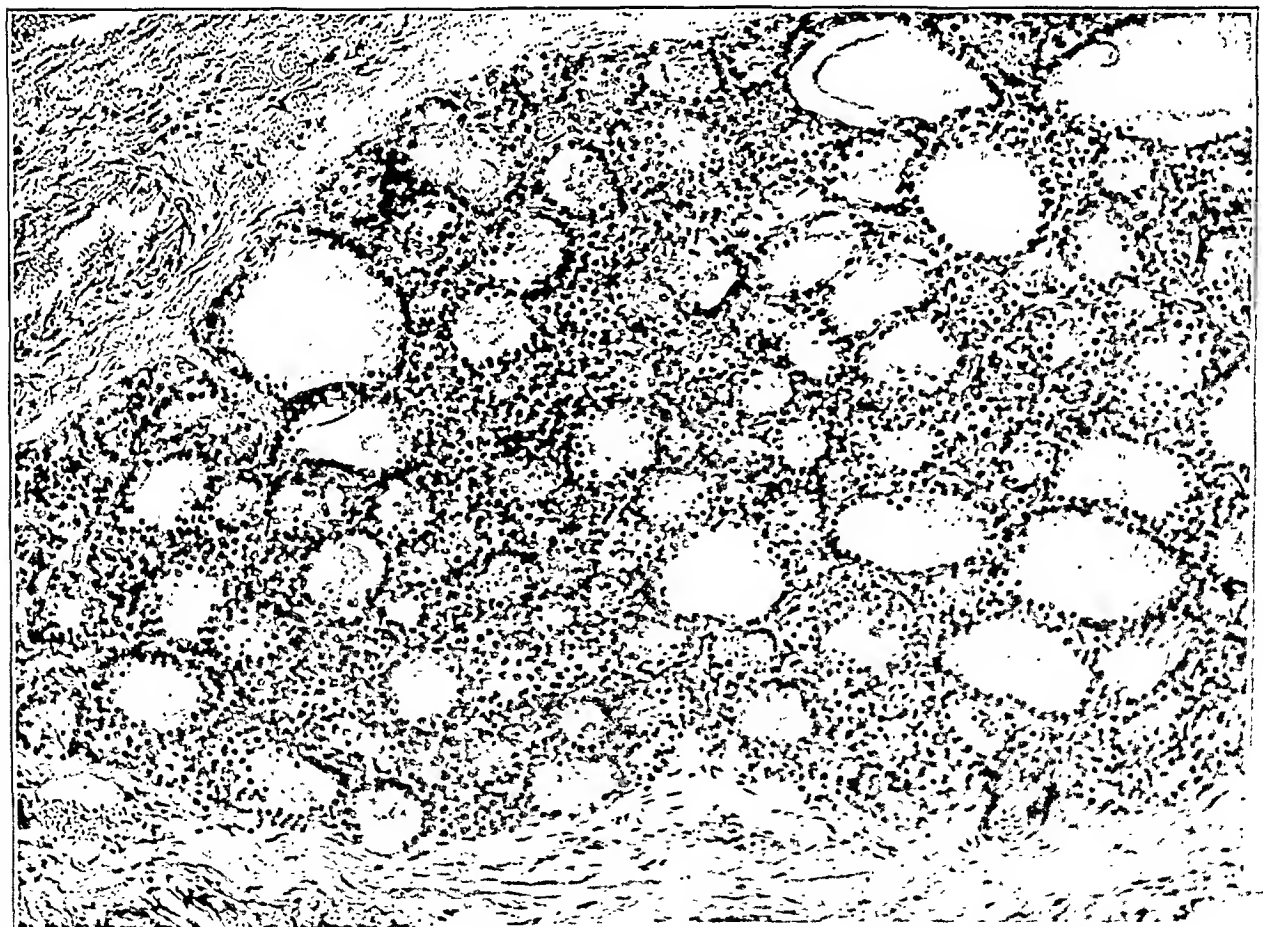


Fig. 7.—Section from a man, aged 75, who died from fractured skull.

acini were small and contained little colloid with scanty inter-acinal connective tissue (fig. 6). Some well developed acini with other areas of undifferentiated epithelial cells and interlobular connective tissue at the periphery were found in the thyroid of a man, aged 75, who died of a fractured skull (fig. 7).

If the foregoing pathologic changes are so variable, there is little wonder that considerable confusion arises in making an accurate diagnosis in definite goiters. In a previous paper⁴ cases were reported in which the clinical diagnosis was of one type of goiter but the pathologic report was of a different type, and if these cases are carefully studied it can be seen that the clinical diagnosis without the knowledge of the pathologic changes was correct; the same holds true for the pathologic diagnosis. The following cases will illustrate the difficulty encountered in making the clinical and pathologic diagnosis coincide.

REPORT OF CASES

CASE 1.—A girl, aged 13 years, first seen by me on July 29, 1930, stated that two years previously her mother had noticed a slight swelling of her neck. Her school physician had advised iodide salt, which she used until April, 1930. Not noticing any improvement in her condition, she consulted Dr. Pohlmann of Middletown, N. Y., on April 9, 1930. Her weight was then 117½ pounds (53.3 Kg.), the pulse 82, and there were no symptoms of hyperthyroidism. Dr. Pohlmann's diagnosis was adolescent goiter. Syrup of ferrous iodide, 10 minims (0.6 cc.), three times a day, was prescribed. On June 12 the weight was 107½ pounds (48.7 Kg.), the pulse rate 84, and still there were no symptoms of hyperthyroidism; the iodide was continued. On June 30, the pulse rate was 120, and there was definite evidence of hyperthyroidism. The iodide medication was discontinued; the patient was put to bed and given 30 grains (1.95 Gm.) of triple bromides every four hours. The basal metabolic rate on July 2, was plus 64. On July 15, the patient was slightly improved but mentally confused, and the basal metabolic rate was plus 25. Rest in bed and bromides were continued. On July 22, her mental condition continued the same, the basal metabolic rate being plus 27. An operation was advised, and she entered the Post-Graduate Hospital on July 29, at which time she was 35 pounds (15.9 Kg.) underweight, her best weight being 127 pounds (57.6 Kg.), as against 93 (42.2 Kg.) on entering the hospital. She was irrational, and physical examination revealed a definite exophthalmic goiter. A partial thyroidectomy was done on August 5. Convalescence was uneventful, and the patient was discharged from the hospital on August 14.

The pathologic report was: diffuse parenchymatous exophthalmic goiter (fig. 8). This case was one of typical adolescent goiter which was changed into an exophthalmic goiter by iodine medication.

CASE 2.—A nurse, aged 38, was first seen by me on Aug. 4, 1927; she stated that twelve years previously she had been operated on for an adenoma of the isthmus of the thyroid. About one year after this operation she noticed a lump in the right side of her neck. This had increased slightly in size, and about seven weeks before consulting me she had a gastro-intestinal upset from eating sea food. Since

4. Hinton, J. William: The Interchangeable Types of Goiter, *Am.J.Surg.* 7: 313 (Sept.) 1929.

that time she had lost 20 pounds (9 Kg.) in weight, and had palpitation of the heart and shortness of breath on going up stairs. Otherwise she felt well. Her menstrual periods had been scanty during the last few months. Examination revealed no evidence of exophthalmos in the right eye. The left eye had been enucleated following an accident at the age of 2 years. At the time of examination there was a nodular mass involving the right lobe without a thrill, and the pulse rate was 108. A diagnosis of adenoma of the thyroid with hyperthyroidism was made. On August 4, the basal metabolic rate was plus 45. The patient

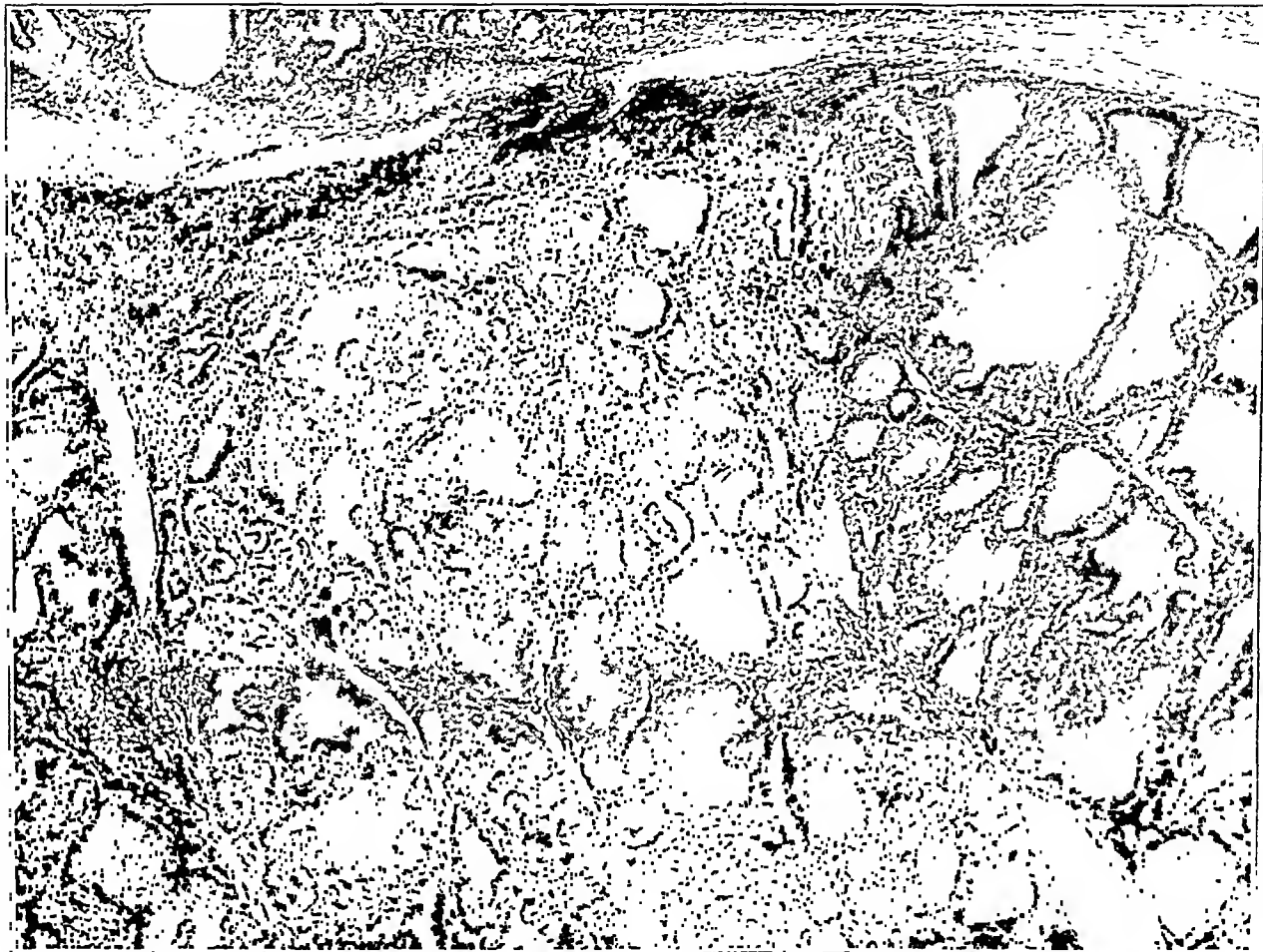


Fig. 8.—Infolding of epithelium in alveoli and little colloid.

was advised to enter the hospital for operation, which she did, and was operated on on August 22. She made an uneventful recovery, being discharged from the hospital on August 30.

The pathologic report was hyperplastic exophthalmic goiter in a stage of remission at the time (fig. 9). This case was considered one of typical adenomatous goiter with hyperthyroidism, and an exophthalmic goiter was not suspected until the pathologic report was received.

CASE 3.—A woman, aged 26, was first seen by me on Nov. 30, 1927, complaining of a swelling in her neck which she had had for one year. Friends first noticed a lump in the right side of her neck, but at that time she had no symptoms refer-

able to goiter. Occasionally sensations of pressure and choking were noticed, but otherwise she felt well. Examination gave negative results, with the exception of a definite mass involving the right lobe of the thyroid. The left lobe was normal. Her weight was 133¾ pounds (60.4 Kg.), and her pulse rate 100. Diagnosis of adenoma of the thyroid was made. On Dec. 2, 1927, the basal metabolic rate was plus 3. The patient was informed that she had the type of goiter that could not be treated by medication, but as I had treated her sister for a colloid goiter with a satisfactory result, she demanded medication before submitting to an operation;

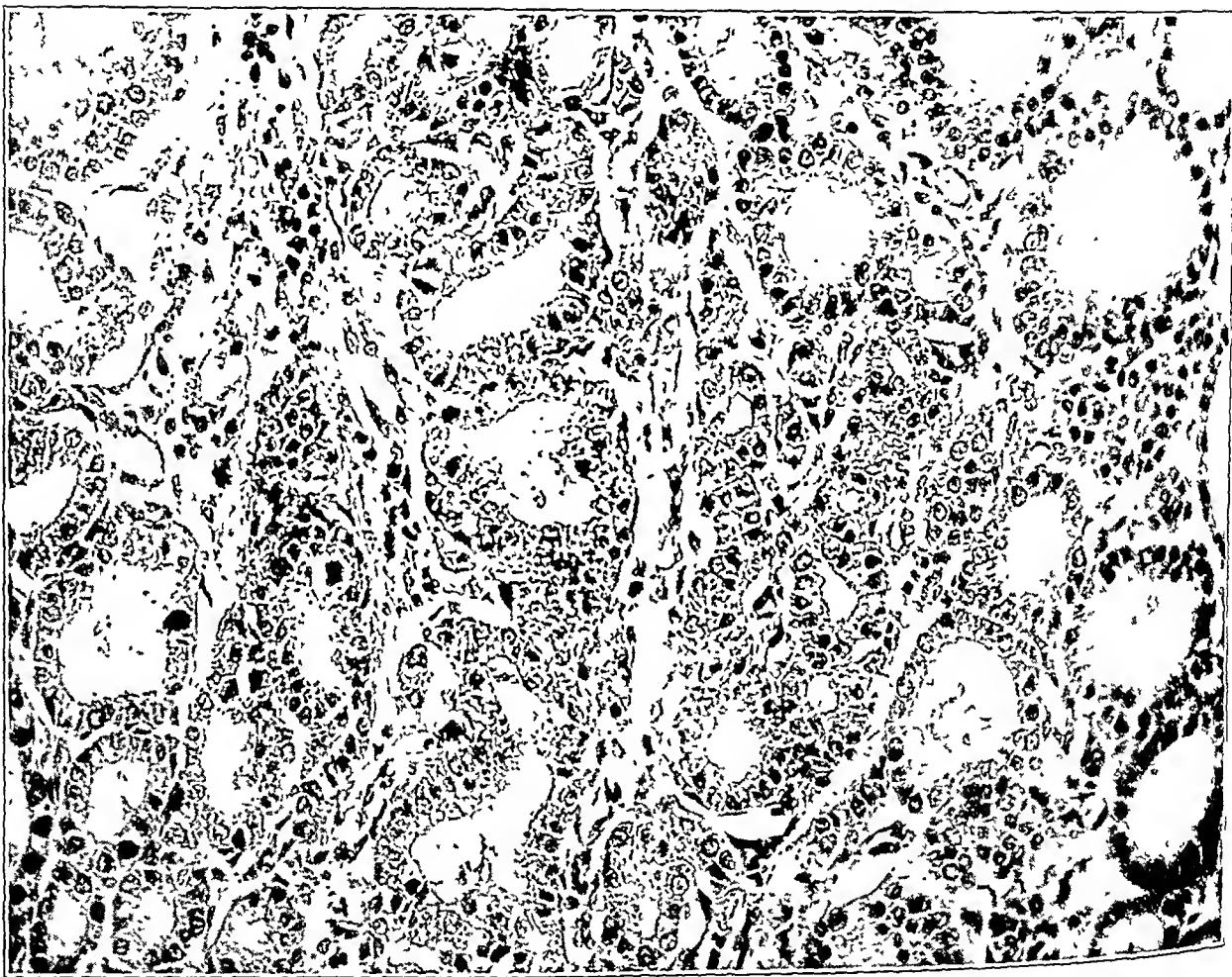


Fig. 9.—Diffuse epithelial hyperplasia with high columnar epithelium, narrow lumen with infolding and with little colloid; active stage.

hence she was given thyroid extract, 1 grain (0.065 Gm.) three times daily. She was next seen on Jan. 18, 1928, at which time her weight was 137¾ pounds (62.2 Kg.) and her pulse rate 90. She had no complaints, but the condition of her neck remained unchanged. She was given thyroid extract, one-half grain (0.32 mg.), three times daily. On March 21, she returned stating she had nausea and vomiting, had been bothered with diarrhea for two weeks and was beginning to feel ill. She complained of nervousness and palpitation, and was losing weight. Examination revealed an enlargement over the region of the thyroid with a definite thrill over it, and a beginning exophthalmos. Diagnosis was then made of



Fig. 10.—Diffuse epithelial hyperplasia. Some areas show narrow alveoli with little colloid and high epithelial lining, others contain much colloid; numerous lymph follicles are seen in the stroma.

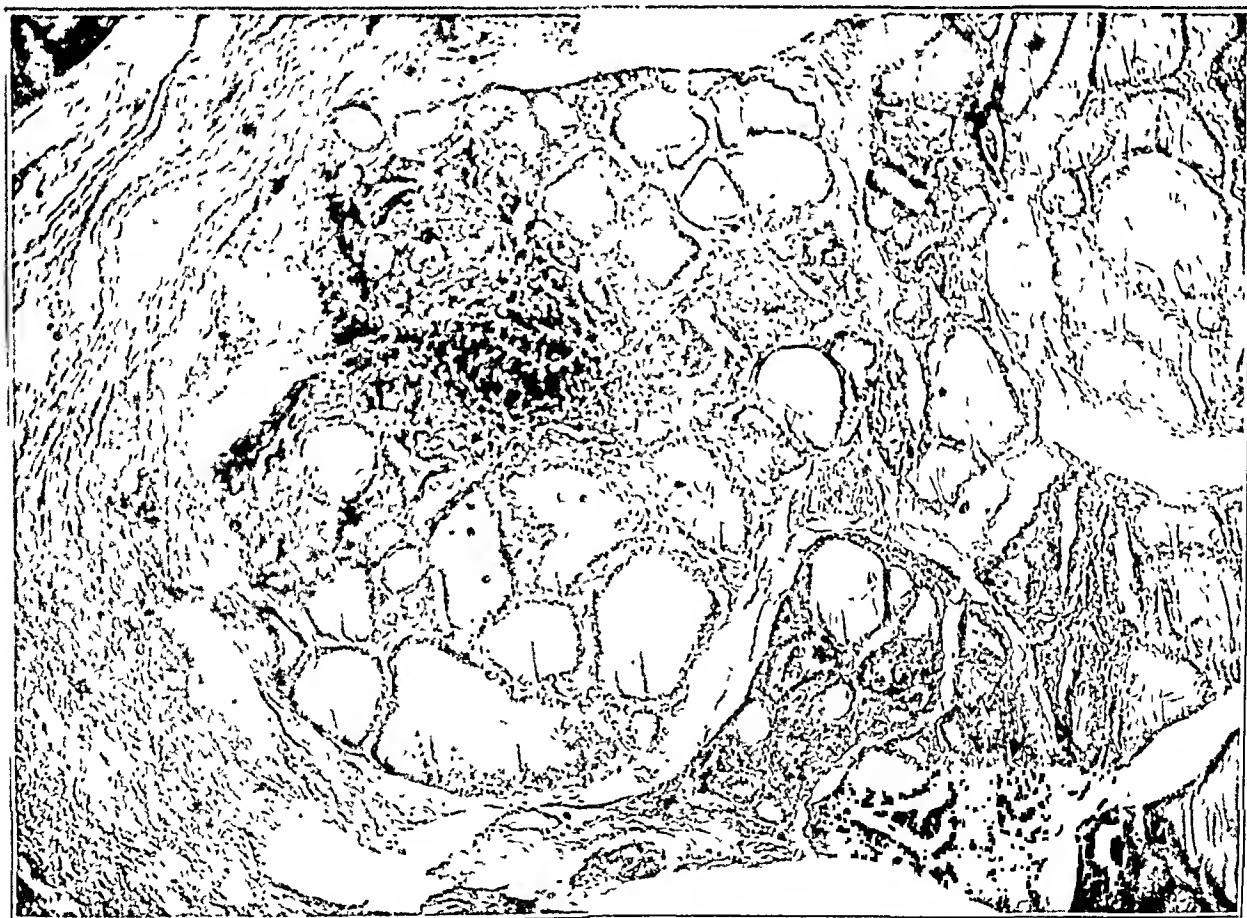


Fig. 11.—Diffuse epithelial hyperplasia with infolding, in some areas more marked than in others. Lymph follicles are seen in the stroma.

exophthalmic goiter. The patient was advised to enter the hospital for observation and operation, which she did on March 22, 1928. On March 26, the basal metabolic rate was plus 60. The weight was 105 pounds (47.6 Kg.) and the pulse rate was 160. The patient was operated on on April 2, and made an uneventful recovery.

The pathologic report was exophthalmic goiter in the stage of remission (fig. 10). From the course of this case one can see a nodular type of goiter changed clinically to an exophthalmic goiter by thyroid medication.

CASE 4.—A woman, aged 33, stated that in September, 1927, she consulted her physician for a swelling of her left ankle and a goiter. At that time she was found to have a phlebitis of the left ankle. On communicating with her physician, Dr. Felder, I found the patient had a colloid enlargement of her thyroid, without symptoms. She was not given any thyroid or iodine medication, but five months later, as her mother had died from an exophthalmic goiter, she consulted a thyroid specialist in New York, for she was rather conscious of the slight fulness in her neck. There were no symptoms referable to the thyroid at that time. On February 4, 1928, the basal metabolic rate was minus 1. The patient was informed that she had no thyroid disturbance, but was given a compound solution of iodine, 3 minims (0.18 cc.) three times a day. Three months later she had lost 8 or 10 pounds (3.6 or 4.5 Kg.) in weight, her eyes were enlarged and she was nervous and quite irritable, and bothered with palpitation. She consulted another physician who told her she had exophthalmic goiter. She was given 1 grain of mercuric iodide once a day and advised to have roentgen therapy. She received several treatments and showed improvement, but four months later, as she was not feeling entirely well, she consulted Dr. Carter, at which time her weight was 118 pounds (53.5 Kg.), as against her best weight of 135 pounds (61.2 Kg.). On October 27, the basal metabolic rate was 3 below the average normal. I saw this patient in consultation with Dr. Carter on October 28, at which time there was definite evidence of enlargement of the thyroid with a thrill over it, and it was quite apparent that the patient was suffering from an exophthalmic goiter. Thyroidectomy was performed on November 5, by Dr. Carter.

The pathologic diagnosis was exophthalmic goiter in the resting stage (fig. 11). In this case one sees a colloid goiter which was changed to the exophthalmic type by the administration of iodine.

COMMENT

When the normal picture is so variable and the clinical and pathologic pictures of different types of goiter are interchangeable, it makes one wonder if the past conception of the different types as clinical entities was not wrong and the types merely represented stages of a continuous disease, as maintained by Hertzler. If so, the treatment of goiters might be simplified, and instead of there being medical treatment for one type and surgical treatment for another, the patient should first be treated medically, if after careful physical examination and metabolic studies there is no evidence of an encapsulated tumor, hyperthyroidism or symptoms of pressure which constitute definite indications for surgical intervention.

HEPATOGENOUS CHOLECYSTITIS *

EDMUND ANDREWS, M.D.

AND

LEO HIRSHNA

CHICAGO

The route of infection to the gallbladder has been studied by many observers, and three possible sources of infection have long been recognized as likely. The well known fact that the blood in bacteremia passes many organisms into the bile has been used by many observers as an argument in favor of the biliary origin of cholecystitis. Others are inclined to favor the hematogenous theory, largely on account of the experiments of Rosenow¹ on the elective localization of certain strains of streptococci. More recently, the studies of Graham² and his co-workers on the absorption of dyes or particulate matter from the region of the gallbladder has brought into prominence the possibility of a carrying of bacteria in the lymph to the gallbladder from the adjacent viscera, especially the liver.

Recent studies on the bacterial flora of the normal liver have again suggested the importance of the latter route of infection, i. e., by direct extension from the liver. In 1909, Wollbach and Saiki³ described an anaerobic spore-forming bacillus as a common inhabitant of livers of normal dogs. In 1927, Berg, Zaw and Jobling⁴ confirmed these observations, although they found the bile uniformly sterile. More recently, Ellis and Dragstedt⁵ have shown that the death from autolysis of the liver in vivo was due to infection of the implanted material with this bacillus, and that sterile implanted liver did not produce any toxemia in its autolysis. Rewbridge⁶ showed that the so-called biliary

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* From the Department of Surgery, the University of Chicago.

1. Rosenow, E. C.: Focal Infection and the Localization of Bacteria, *Surg. Gynec. Obst.* **33**:19, 1921.

2. Graham: Inflammation Accompanied by Cholecystitis, *Surg. Gynec. Obst.* **26**:521, 1918.

3. Wollbach, S. B., and Saiki, Tadasee: A New Anaerobic Spore-Bearing Bacterium Commonly Present in the Liver of Healthy Dogs, *J. M. Research* **21**: 267, 1909.

4. Berg, B. N.; Zaw, Z. D., and Jobling, J. W.: Bactericidal Function of Liver, *Proc. Soc. Exper. Biol. & Med.* **21**:433, 1927.

5. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis in Vivo, *Arch. Surg.* **20**:8 (Jan.) 1930.

6. Rewbridge, A. G.: Etiological Rôle of Bacteria in Bile Peritonitis, *Proc. Soc. Exper. Biol. & Med.* **27**:528, 1930.

peritonitis was due to this organism, and that intraperitoneal injection of sterile bile or even of sterile pure bile salts was capable of producing an infection by this organism. We⁷ also showed that implantation into the abdomen of normal animals of sterile liver or liver extract, if the material was finely divided, would provoke such an infection. Careful bacteriologic studies of this organism in our laboratory have shown that it is without a doubt the Welch bacillus (published elsewhere). It has been found in over 200 experiments in both dogs and other animals. Finally, we wish to refer to the experiments of Arnold⁸ in which he showed that under quite physiologic conditions of digestion there is a passage of bacteria through the intestinal wall so free that they may be found in the lymph of the thoracic duct in numbers as high as 1,000 per cubic millimeter. With this enormous seeding of the tissues with bacteria, which must occur daily, one assumes that it is but natural that the spore-bearers should be more resistant to destruction and that they should be the predominant element in the flora. The comparative richness of the flora of the liver is, of course, due to the fact that bacteria, being particulate matter, are taken up by the reticulo-endothelial system, which is so largely localized there.

In the preparation of jaundiced dogs for some experimental studies on jaundice, it was observed that the mortality rate was high and out of proportion to the severity of the operation, and that in some cases frank cholecystitis had developed. This was especially noted in those dogs that had had the cystic duct ligated and the gallbladder emptied, as recommended by Rous and McMaster⁹ in their preparation for biliary fistulas. Empyema of the gallbladder in one case and culture of *B. welchii* from another prompted the following series of experiments.

EXPERIMENTAL WORK

With these points in view, a series of twenty-five dogs were studied in which biliary stasis had been produced. Twelve dogs had a simple ligation of the cystic duct. In this series extreme care was used to avoid the cystic artery. This is much easier in dogs than in man, as the artery joins the gallbladder at a greater distance from the common duct. In five dogs the common duct was ligated near the duodenum and in six both the common and the cystic duct were ligated. In two, the common duct was ligated, and, in addition, bilateral nephrectomy was performed in order to increase the intensity of the jaundice.

7. Andrews, E., and Hrdina, L.: Liver Autolysis in Vivo, Proc. Soc. Exper. Biol. & Med. **27**:987, 1930.

8. Arnold, L.: Alterations in the Endogenous Enteric Bacterial Flora and Microbic Permeability of the Intestinal Wall, J. Hyg. **29**:82, 1929.

9. Rous, P., and McMaster, P. D.: Sterile Drainage of Intraabdominal Ducts as Applied to the Common Duct, J. Exper. Med. **37**:11, 1923.

These dogs were killed at various intervals from twenty-four hours to two months, the bile cultivated, and histologic examinations of the gallbladder made. The dogs were all killed by electrocution, and the cultures were made at once in order to rule out any possibility of postmortem contamination. In many cases sections of the liver were made as well, and in one series the gallbladder and adjacent liver fixed en masse so as to get continuous sections of the two.

RESULTS

The results of the cultures are shown in the table. As a control for this work, the reader is referred to the paper by Rewbridge,⁶ who

Cultures of Bile in Dogs

Dog	Operation	Duration of Experiment	Culture
Dogs With Biliary Stasis			
8	Ligation of cystic duct..	17 days	B. welchii
11	Ligation of cystic duct..	1 month	Diplococci
14	Ligation of cystic duct..	3 days	B. welchii and streptococci
16	Ligation of cystic duct..	3 days	B. welchii, streptococci and staphylococci
17	Ligation of cystic duct..	3 days	B. coli
27	Ligation of cystic duct..	3 days	Staphylococci
26	Ligation of cystic duct..	3 days	B. welchii
92	Ligation of cystic duct..	57 days	Diplococci
90	Ligation of cystic duct..	6 days	Sterile
95	Ligation of cystic duct..	57 days	Sterile
144	Ligation of common duct..	3 days	Staphylococci
145	Ligation of common duct..	3 days	Diplococci
146	Ligation of common duct..	3 days	Diplococci
147	Ligation of common duct..	3 days	Staphylococci
149	Ligation of common duct..	3 days	Diplococci
802	Ligation of common and cystic ducts..	1 day	B. welchii
813	Ligation of common and cystic ducts..	20 days	B. welchii and diplococci
820	Ligation of common and cystic ducts..	8 days	B. welchii
831	Ligation of common and cystic ducts..	8 days	B. welchii
834	Ligation of common and cystic ducts..	3 days	B. welchii
836	Ligation of common and cystic ducts..	12 days	Diplococci
Dogs With No Pathologic Process			
955	Ligation of cystic duct..	Culture taken 24 hours after operation	B. welchii
956	Ligation of cystic duct..	Culture taken 24 hours after operation	Sterile
957	Ligation of common duct and bilateral nephrectomy	3 days	B. welchii
958	Ligation of common duct and bilateral nephrectomy	3 days	B. welchii

showed that in our laboratory at least the bile of normal dogs is uniformly sterile. This agrees with the observations of most other investigators, although exceptions have been noted. It depends, one may assume, on the conditions under which the dogs are kept as well as on the technic of making the cultures. In the normal dog, the wall of the gallbladder is often found infected or at least containing organisms, but the bile is usually sterile.

The results of the cultures in the different series may be summarized as follows:

1. In the series in which the cystic duct was ligated, seven of the twelve dogs showed *B. welchii*, five cocci and colon bacilli and only two were sterile.

2. In the series in which the common duct was ligated all showed cocci, and in the two in which double nephrectomy was added, *B. welchii*.

3. In the series in which both ducts were ligated, five of the six showed *B. welchii* and three cocci, all having some infection.

It is evident, therefore, that the presence of biliary stasis favors the prompt infection of the bile and that the predominant flora is that of the liver, the anaerobic type.

The pathologic changes in these experiments are of great interest, as they revealed the fact that the resulting inflammation of the gallbladder which occurred in about two thirds of the cases was undoubtedly of hepatic origin. In the early stages of the cholecystitis in a number

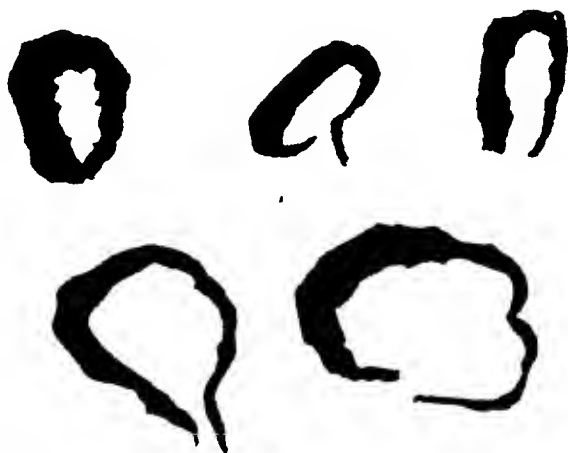


Fig. 1.—Series of sections through fixed gallbladders showing unilateral thickening of the walls. This discrepancy is even more marked in the fresh tissue. Hepatic surfaces are seen to the left.

of the cases the inflammation was confined to the hepatic surface of the viscus while the peritoneal or free side was quite normal. In the later stages this infection extended all the way around the gallbladder. Some of such unilaterally inflamed gallbladders are shown in figure 1. These are all taken from material which has been run through fixatives so that considerable contraction has taken place and the disproportion between the two sides is not as marked as in the fresh specimens. It is quite apparent, however, that the hepatic surfaces are very much more thickened than the free surfaces. Figure 2 is a photograph of a fresh specimen in which the unilateral nature of the process is still more obvious. This phenomenon is much more marked in cases in which the cystic duct has been ligated, but following ligation of the common duct it can be seen to a lesser degree grossly and is quite evident microscopically. In the cases in which the common duct has

been ligated its onset is also more delayed, while in obstruction of the cystic duct it begins at once and can best be demonstrated about the third day, although changes can be seen in twenty-four hours.

Figure 3 illustrates the appearance under very low power magnification of such a specimen. The hepatic surface can be seen to be about three times as thick as the free side. The inflammation involves the outer coats for the most part. The muscularis is thickened to a much lesser extent, and the mucosa is nearly normal. On the peritoneal side the mucosa is normal, as is the muscular coat, but there is a slight thickening of the serous layer.

In all cases it is evident that the mucosa is the last of the coats to be involved. Figure 4 shows the mucosa under higher power magnification; it is quite free from infiltration, although in the same



Fig. 2.—Photograph of a fresh specimen showing thickening of the hepatic surface but not of the peritoneal surface. Note the gelatinous edema of the space between the gallbladder and the liver.

gallbladder the edge of the liver and tissues between the liver and gallbladder were edematous and infiltrated with leukocytes. Even in the later stages the outer layers of epithelial cells tend to remain normal while there is a collection of round cells and fewer polymorphonuclears in the submucous follicles (fig. 5). This condition is never extensive, and only a few such follicles were found in our entire series; they are occasionally to be seen in the gallbladders of normal dogs, although not quite so extensively as in the one here pictured.

The earliest lesions to be found are in the margins of the liver adjacent to the gallbladder and in the space between the gallbladder and the liver. This space often becomes exceedingly edematous, and even grossly can be seen as a gelatinous layer 0.5 cm. thick. In this space bacteria were seen in many of our preparations. Cellular infiltration of this tissue soon follows, as illustrated in figure 6. This may



Fig. 3.—Hepatic surface below. Note the unilateral thickening of the outer coats of the gall-bladder and the comparative freedom of the mucosa three days after ligation of the cystic duct. Reduced from a magnification of $\times 17$.

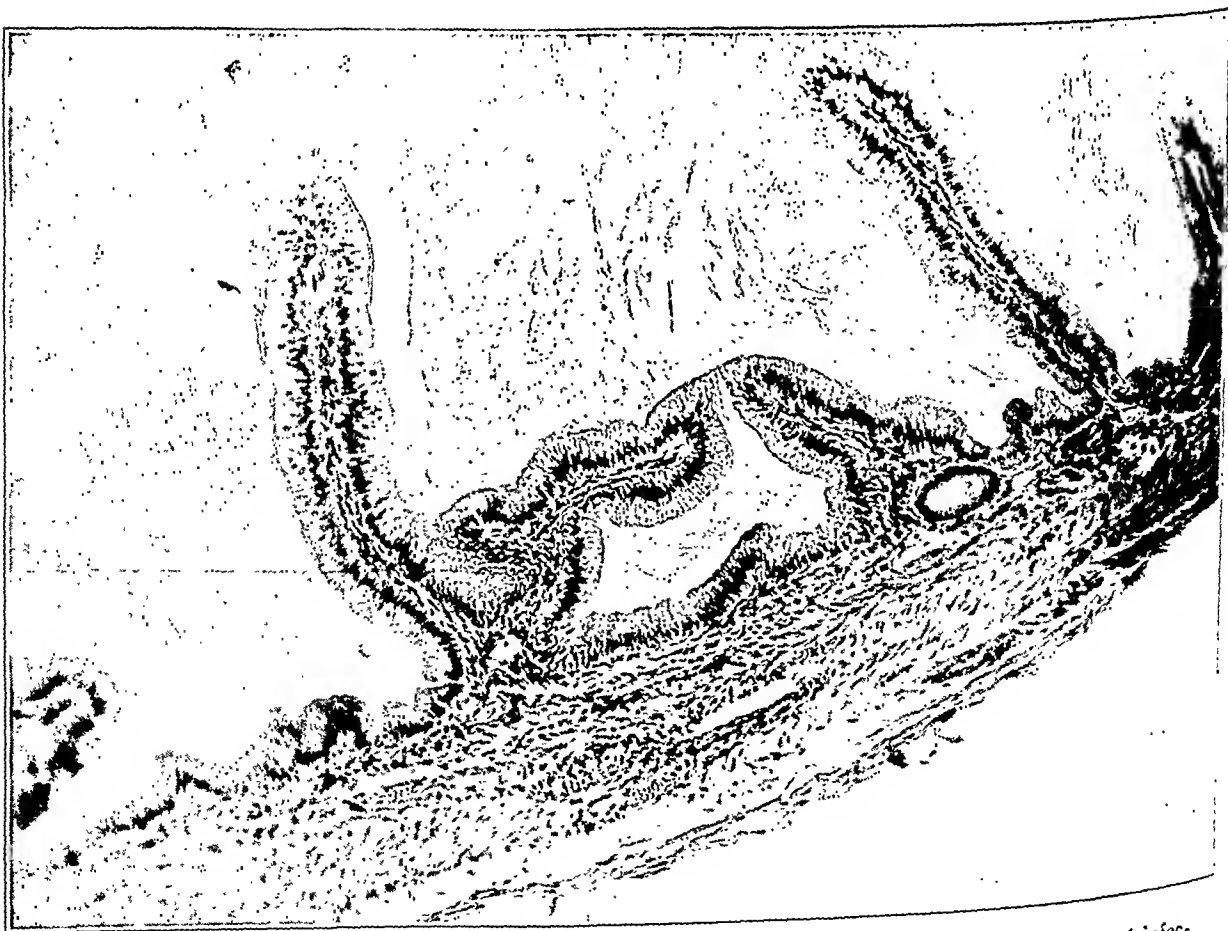


Fig. 4.—Normal mucosa six days after ligation of the cystic duct. There was marked infection from a magnification of $\times 130$.

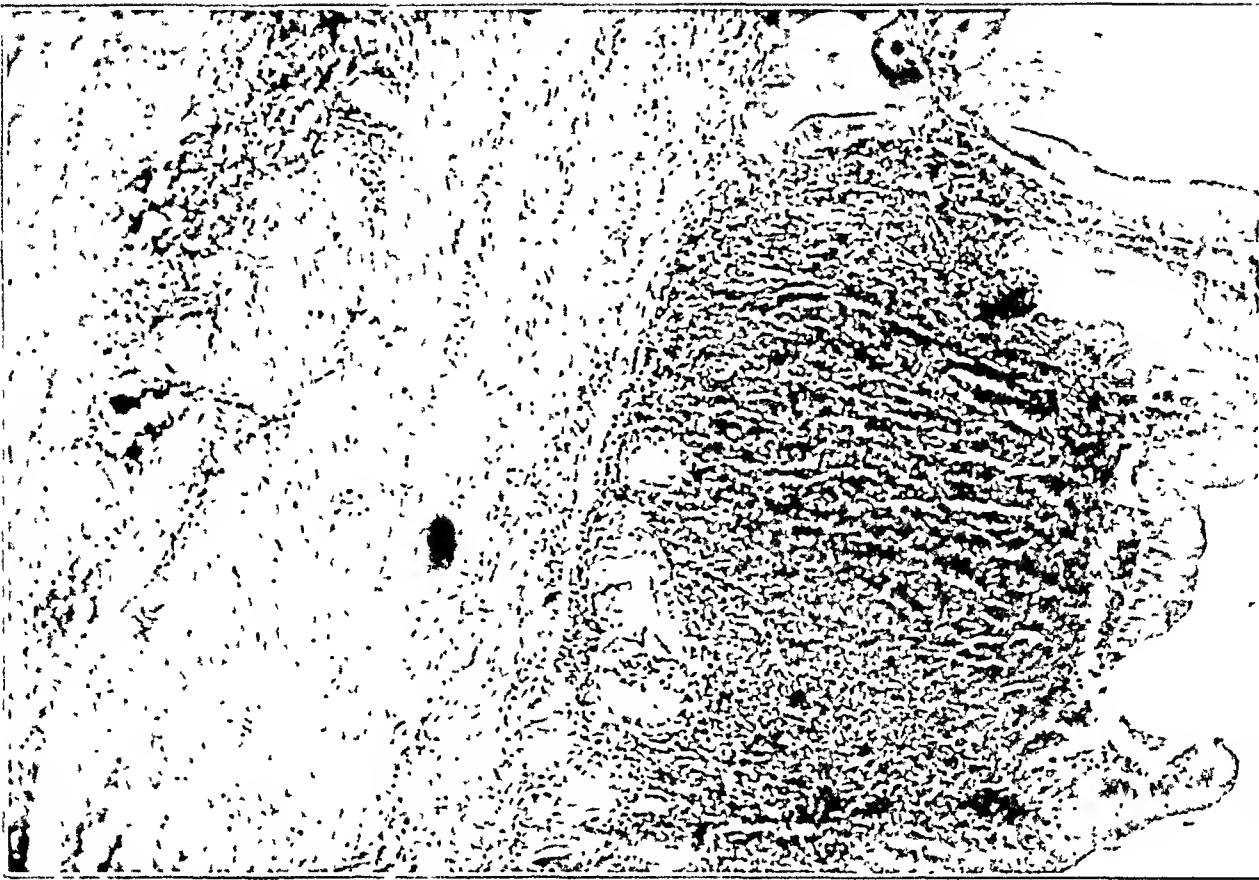


Fig. 5.—Later stage fifty-seven days after operation. A follicle is seen in the submucosa. Reduced from a magnification of $\times 130$.



Fig. 6.—Same as figure 4 showing dense infiltration of hepatic tissue adjacent to the gallbladder and slight infiltration of the tissue between the liver and the gallbladder. Note the normal mucosa. Reduced from a magnification of $\times 130$.

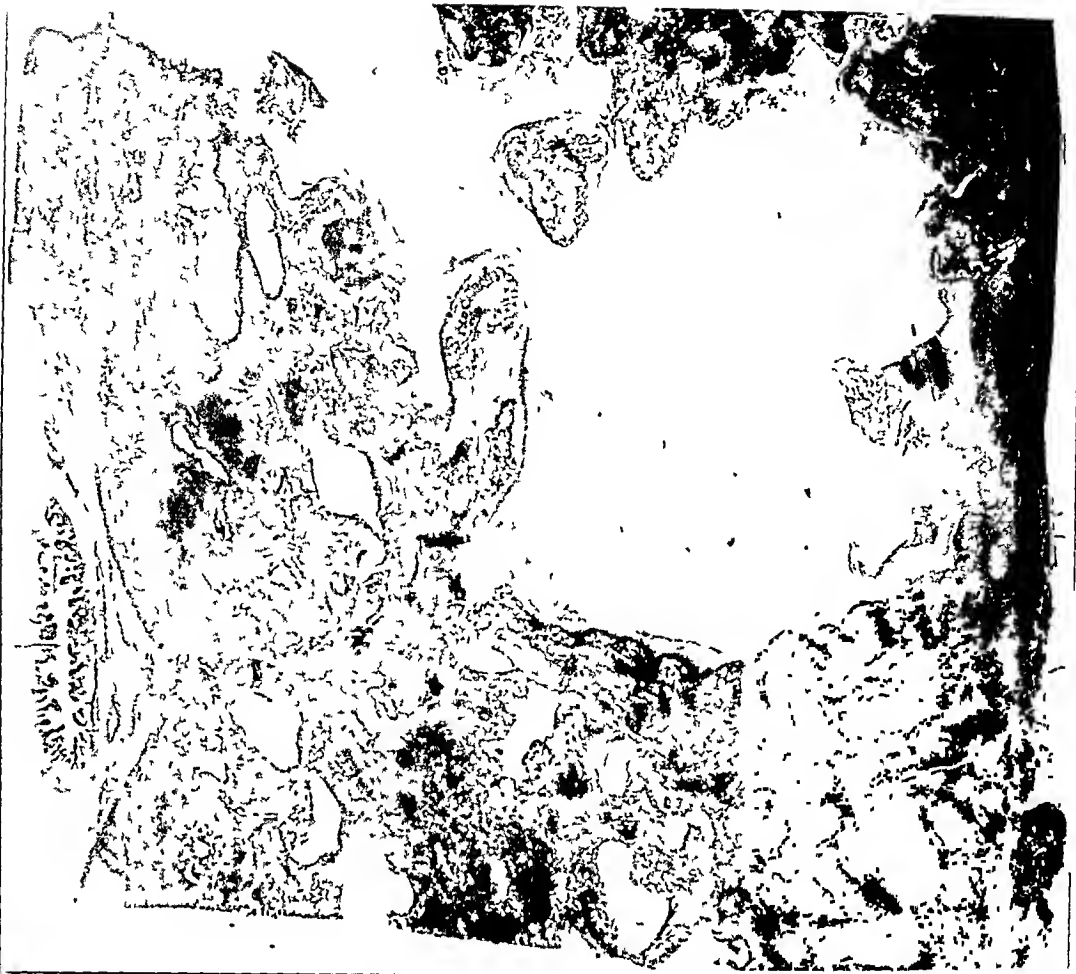
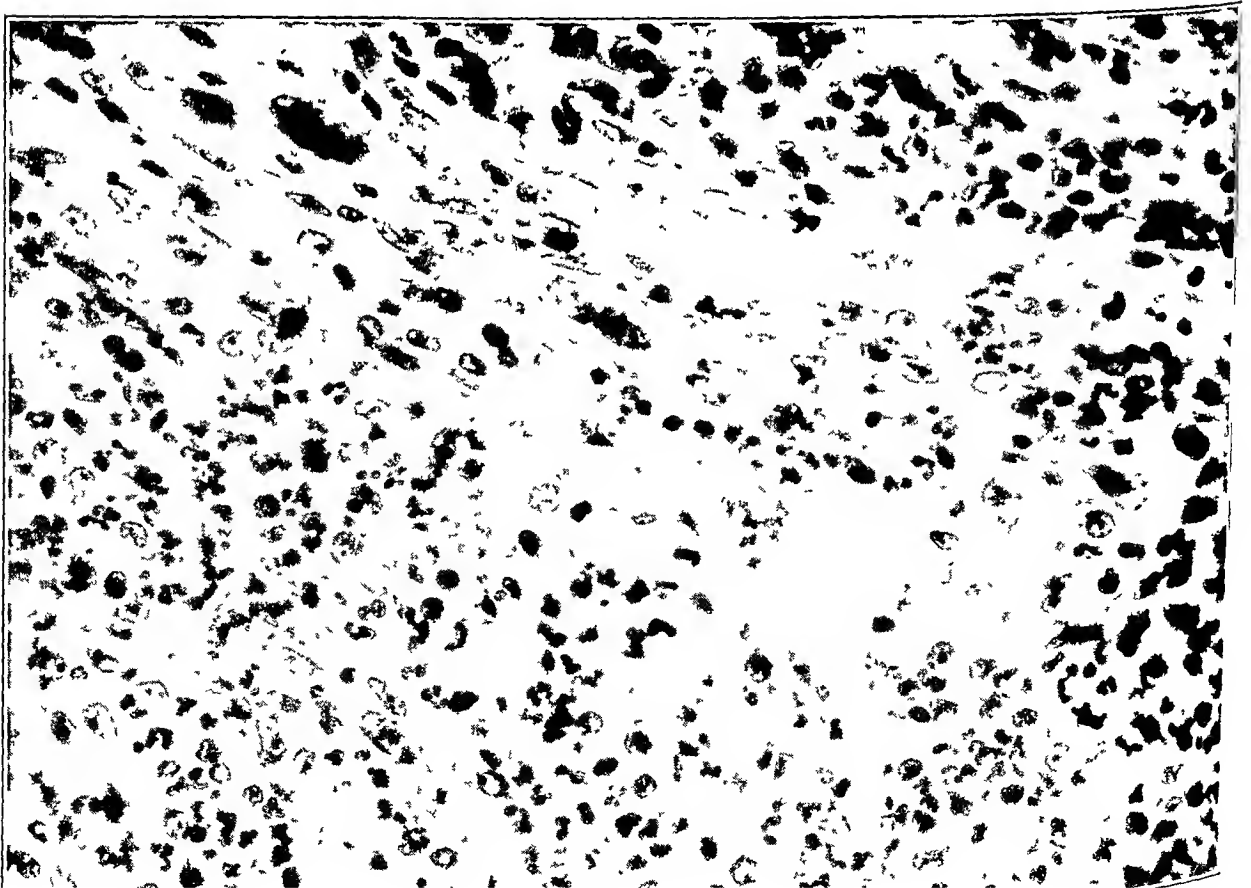


Fig 7 —The hole in the center is the gallbladder. Note how the hepatic tissue is riddled with gas bubbles, $\times 4$.



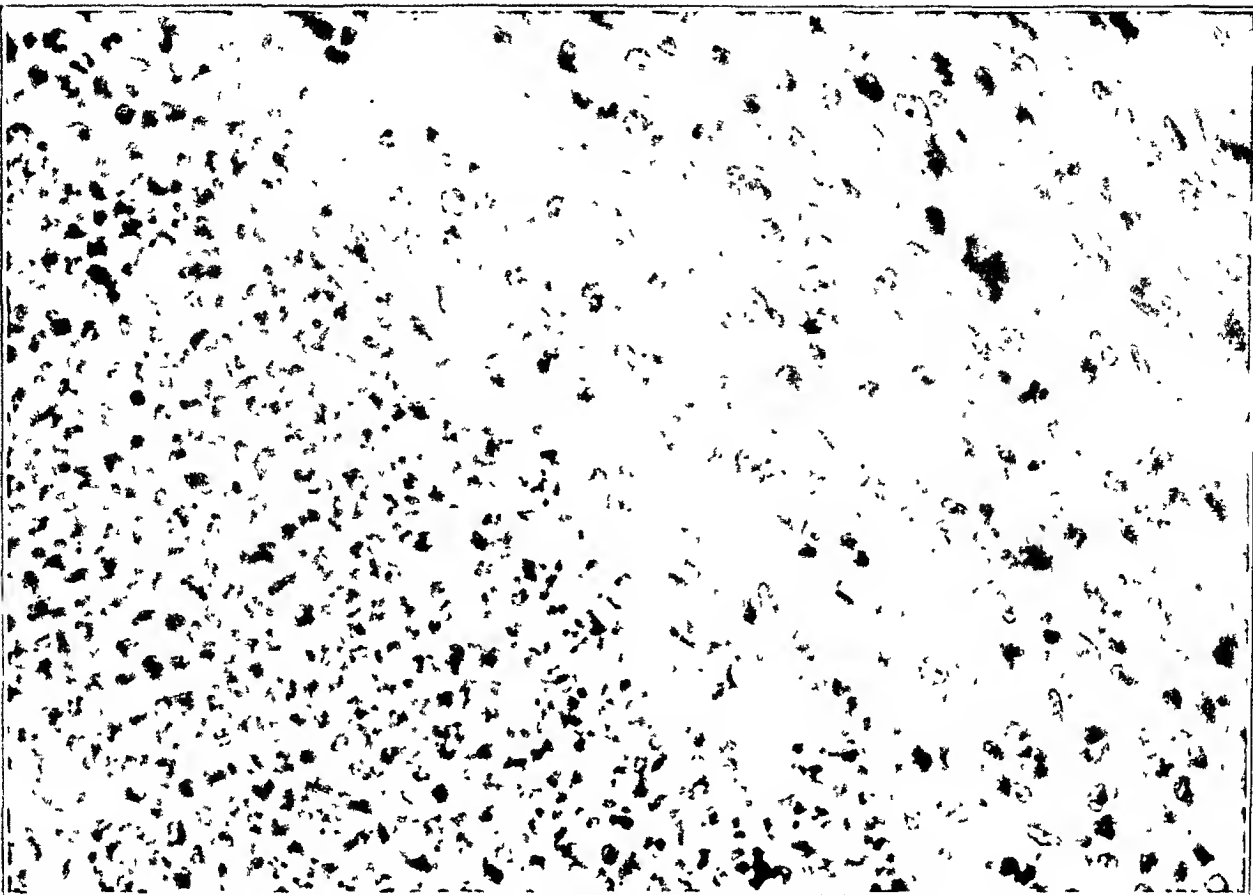


Fig. 9.—Same as figure 8; another field.

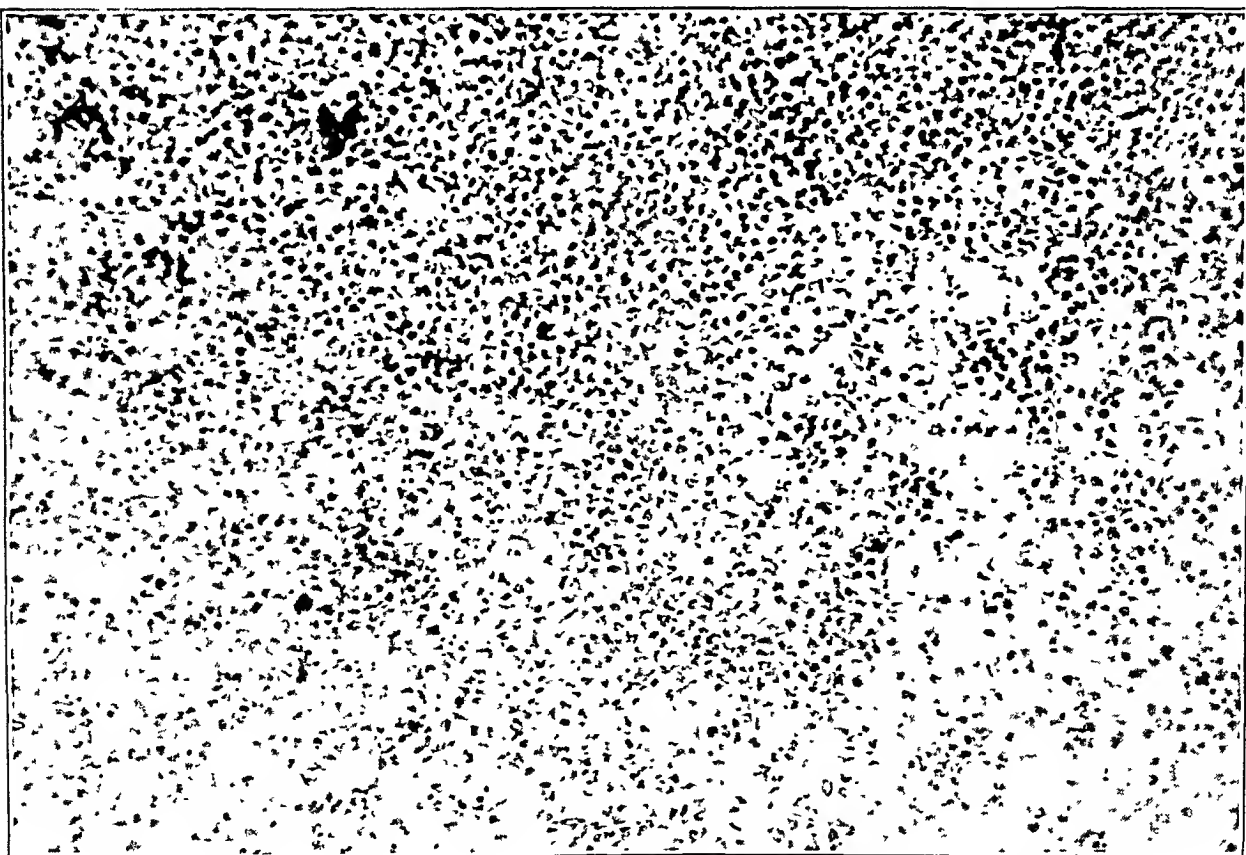


Fig. 10.—Section through muscular walls of the gallbladder four days after ligation of the common and cystic ducts; $\times 300$. Marked cellular infiltration of both round and polymorphonuclear leukocytes is seen. Reduced from a magnification of $\times 300$.

be very dense, and often tiny abscesses are encountered. The infection of the adjacent liver may be extremely severe in time. Even multiple gas-filled abscesses may occur, as shown in figure 7. Examination of the walls of such abscesses shows a dense polymorphonuclear infiltration (figs. 8 and 9) with central necrosis and numerous Welch bacilli as well as cocci in the tissues. The hepatic tissue proper is undergoing marked degeneration. Bile capillaries in the region appear to be con-

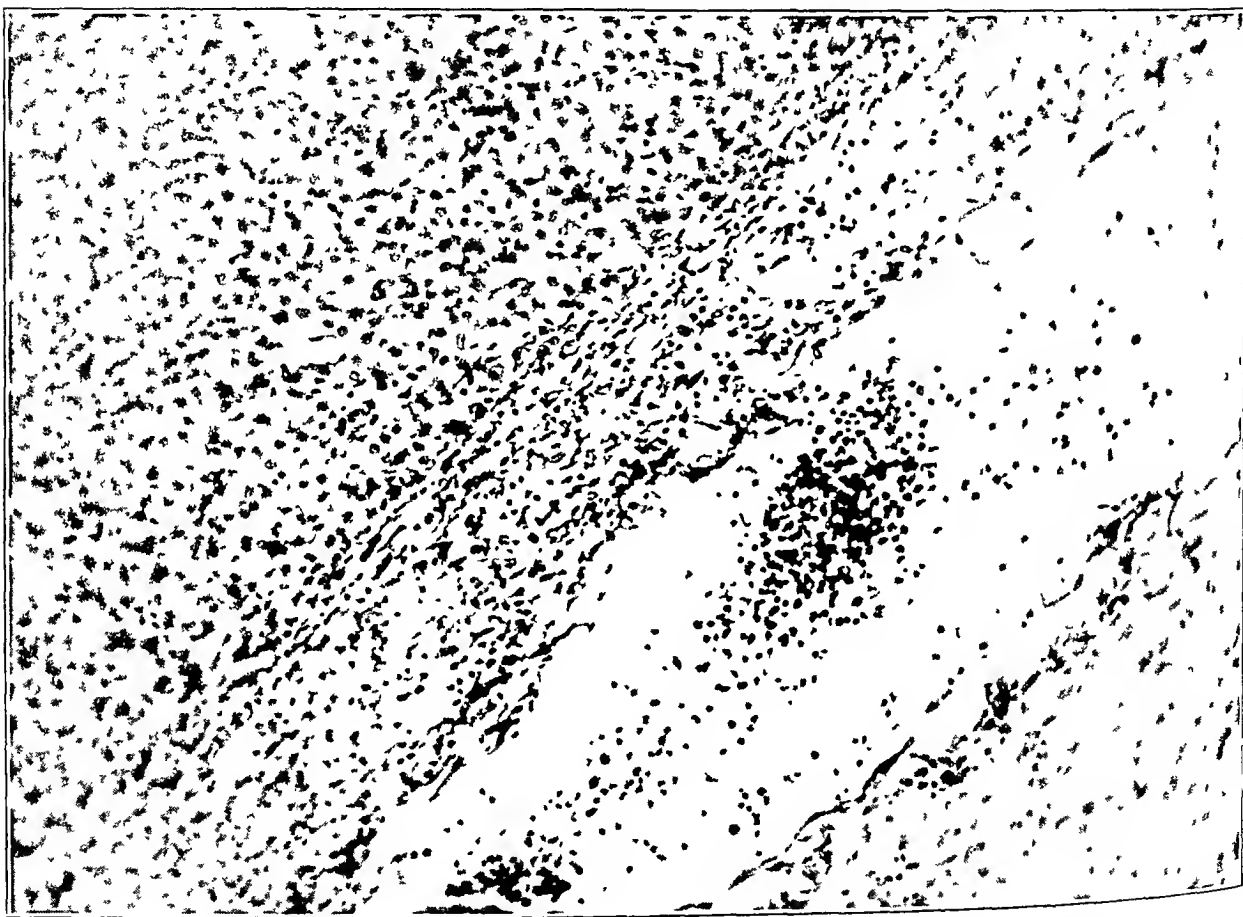


Fig. 11.—Section two months after ligation of the cystic duct; $\times 180$. Note the infiltration of the liver with leukocytes, and the marked edema of the tissues between the gallbladder and the liver with small abscess forming and lesser infiltration of the wall of the gallbladder. Reduced from a magnification of $\times 180$.

spicuously free from involvement in the inflammatory process, as do other parts of the liver.

Infection of the muscular walls of the gallbladder soon takes place. This is manifested by edema (not so marked as in the areolar tissue between the gallbladder and liver) and infiltration of round cells. The polymorphonuclear infiltration is less than in the liver itself in most cases (fig. 10).

As already stated, after ligation of the common duct these changes are not so marked grossly, but histologically they are quite evident. They also begin in the liver and not in the gallbladder.

Figure 11 gives a view of the entire process. The liver shows degenerative change and an invasion of leukocytes. The space between the gallbladder and the liver is markedly edematous and contains a dense localized clump of inflammatory tissue. Leukocytes are also scattered through the edematous area and are beginning to infiltrate the muscular coat of the gallbladder.

COMMENT

The fact that biliary stasis is a factor in the production of cholecystitis has been known for a long time. However, the extent and severity of the accompanying lesions have, I believe, never been called to attention. Walsh and Ivy¹⁰ reported such changes in a recent paper but gave no detailed studies of them. The most important factor is the one here demonstrated that the infection makes its way into the gallbladder by direct extension from the liver, and in the early stages, especially, the characteristic flora is that of the liver. Many of the bacteriologic studies that have been made can be criticized on the basis that special mediums were used in the search for streptococci, and that the anaerobic organisms have not been sought. Ever since Rosenow's reports on the localization of intravenously injected streptococci, these organisms have received special attention. Williams and McLachlan¹¹ have recovered them from many human cases but could demonstrate no specificity. The elaborate experiments of Wilkie¹² on the production of experimental cholecystitis ignored all other organisms, although in rabbits, the animals they used, the livers contain an especially rich anaerobic flora.

The importance of anaerobes has recently been emphasized by Whitby and Gordon-Taylor.¹³ In an extensive review of the literature it is shown that the occasional occurrence of *B. welchii* in series of cultures of the gallbladder in cholecystitis is reported by many observers, although this observation seems usually to be considered as incidental. In their series, anaerobes were found in considerably higher percentages

10. Walsh, E. L., and Ivy, A. C.: Etiology of Gallstones, *Ann. Int. Med.* **4**:134, 1930.

11. Williams, B., and McLachlan, D. G. S.: Etiology of Cholecystitis, *Lancet* **2**:342, 190.

12. Wilkie, A. L.: The Bacteriology of Cholecystitis, *Brit. J. Surg.* **15**:450, 1930.

13. Whitby, L. E. H., and Gordon-Taylor, G.: A Bacteriological Study of Fifty Cases of Cholecystitis, *Brit. J. Surg.* **18**:78, 1930.

than that reported by previous observers, in 13 per cent of the gallstones and 9.5 per cent of the gallbladders. They emphasize the fact that it is in the acute fulminant or gangrenous gallbladder that *B. welchii* are encountered. The use of antiserum is recommended, and they recognize the probable hepatic origin of such types of cholecystitis, from the known anaerobic flora of that viscus.

Since the publication of their paper, there have been five such cases in the Billings Hospital. The patients were so acutely ill and the sepsis so marked that it was not thought safe to wait for a remission. *B. welchii* was found in three of the cases and in two of these the gallbladder was gangrenous. One died within twenty-four hours after the operation.

The association of hepatitis with disease of the gallbladder has long been known. The localized hepatitis about an inflamed gallbladder often produces an apparent mass of hepatic tissue which overhangs the gallbladder, and which on palpation may be mistaken for that organ. In the French literature this has received a special name, "langnette hepaticue." The earlier work of Graham also emphasized the fact that the liver took part in infections of the gallbladder. Bits of hepatic tissue excised at operation show marked evidences of infection. The recent report by Flint¹⁴ confirms these observations, and the latter believes that hepatitis is often the result of lesions in the abdomen other than in the gallbladder.

Else¹⁵ has recently given an admirable summary of the evidence that the gallbladder may be secondarily involved from the liver. He demonstrated experimentally the rapid absorption of particulate matter from the retrocholecystic space into the liver. Attention is called to the work of Meyer, Neilson and Feusier¹⁶ showing that enormous numbers of bacteria must be in the circulation to bring about a very high biliary content, and to Graham and Peterman's¹⁷ experiments showing that usually not enough bacteria pass into a normal gallbladder to produce inflammation, but that stasis or injury to the wall of this organ is necessary. From the foregoing data, Else concluded that hepatic cholecystitis by direct extension is of frequent occurrence.

14. Flint, E. R.: Association Between Gallbladder Lesions and Hepatitis in the Human Subject, *Brit. M. J.* **1**:1041, 1930.

15. Else, J. E.: The Relationship of Hepatitis to Cholecystitis, *Northwest Med.* **29**:252, 1930.

16. Meyer, K. F.; Neilson, N. M., and Feusier, M. L.: Mechanism of Gallbladder Infections in Laboratory Animals, *J. Infect. Dis.* **28**:456, 1921.

17. Graham, E. A., and Peterman, M. G.: Further Observations on Lymphatic Origin of Cholecystitis, *Arch. Surg.* **4**:23 (Jan.) 1922.

The importance of the liver in the defensive mechanism of the body against infection has been emphasized by Heyd.¹⁸ After abdominal operations, especially septic ones, he warns of the danger of infection of the liver with resulting disturbance of the chemical equilibrium of the body and dwells on the necessity of treating a patient with such a deficiency of the liver by proper chemical means. Mueller and Bruett's¹⁹ experiments on the intravenous injection of bacteria show that the reticulo-endothelial system of the liver is the most active agent in the fixation and destruction of circulating micro-organisms, and that other organs become infected only when they are injured. Petersen and Mueller²⁰ have shown that the elimination of bacteria from the blood stream is almost stopped after hepatectomy, while Jaffe²¹ has demonstrated that particulate matter also continues to circulate in the blood stream after hepatectomy, while it is eliminated in a few minutes by the normal animal.

In this connection, the experiments of Badylkes and Strokow²² are of great interest. They showed that infection of the gallbladder in animals caused pylorospasm and hyperperistalsis of the small intestines. The obstruction of the pylorus was at times almost complete. The conditions described must approximate accurately those produced by Arnold and Brody²³ in their experiments. They brought a loop of duodenum up under the skin, so that they could inject material into it or aspirate its contents. When the p_H was 8.0 and egg-white was in the duodenum, the lymph from a fistula of the thoracic duct contained from 500 to 1,000 bacteria per cubic millimeter. Such an enormous feeding of bacteria into the circulation must act in such a manner as to keep the liver constantly seeded, especially as it can be shown to occur under conditions likely to obtain in infections of the gallbladder.

The effect of anesthetics on the liver has long been known, especially the lipid solvent group. Bollman²⁴ has recently reviewed this subject

18. Heyd, C.: Hepatitis, Surg. Gynec. Obst. **39**:66, 1924; Protective Rôle of the Liver in Abdominal Surgery, Am. J. Obst. & Gynec. **19**:203, 1930.

19. Mueller, E. F., and Bruett, H.: Significance of Liver in Natural Defense Against Infections, München. med. Wchnschr. **76**:2044, 1929.

20. Petersen, W. F., and Mueller, E. F.: Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med. **40**:575 (Nov.) 1927.

21. Jaffe, R. H.: The Reticulo-Endothelial System, Arch. Path. **4**:45 (July) 1927.

22. Badylkes, S. O., and Strokow, F. Y.: Cholecystitis: Effect on Motor Functioning of Genito-Urinary Tract, Arch. f. Verdauungskr. **47**: 222, 1930.

23. Arnold, L., and Brody, L.: Passage of Living Bacteria Through the Intestinal Wall, Proc. Soc. Exper. Biol. & Med. **25**:247, 1928.

24. Bollman, J. L.: Effect of Anesthetic Agents on the Liver. Proc. Staff Meet., Mayo Clin. **9**:369 (Dec. 18) 1929.

and called attention to the fact that the liver as seen by the surgeon is generally low in glycogen, and that this increases the toxic effect of anesthetics. He advocated ethylene for operation in such cases. Higgins²⁵ also called attention to the effect of trauma on the liver and found a marked cellular infiltration of the organ. Both of these factors, of course, have an evident bearing on our problem, and in view of the fact that bacteria tend to locate themselves in injured tissue, the importance of such factors in the production of disease of the gallbladder and on the postoperative course in operations on the gallbladder, which involves a field with such a rich flora, may be very great. The recent report of Miller,²⁶ who advocated operation in many cases of cholecystitis in which most surgeons would attempt medical treatment, seems justified in view of our experimental and clinical observations, as in such severe infections due to *B. welchii* immediate drainage is surely indicated if the condition can be differentiated from the other more mild types.

CONCLUSIONS

1. In biliary stasis the gallbladder of the dog promptly becomes infected with the characteristic anaerobic flora of the liver.
2. Pathologic studies at various stages show that this infection occurs by direct extension from the liver.
3. The fulminant type of human cholecystitis is often caused by the Welch bacillus from the liver.

25. Higgins, G. M.: Reaction of the Liver to Trauma, Proc. Staff Meet., Mayo Clin. 5:88 (March 29) 1930.

26. Miller, R. H.: Acute Cholecystitis, Ann. Surg. 92:644, 1930.

FIBROCARILAGINOUS TUMORS OF THE BONE*

CHARLES F. GESCHICKTER, M.D.

BALTIMORE

The derivation of tissues from more rudimentary antecedents, which is the normal method of achieving adult structures in the human body, constitutes a major source for tumor pathology, since it is in such developmental steps that most neoplasms arise. The structure of the tumor often reveals this fact by a cycle of changes similar in form and sequence to the successive stages of normal growth in the portion of the body where it arises.

This is well illustrated by the relation of certain tumors of the bone to the evolution and embryologic development of the skeleton. In its primitive form the early vertebrate spine (notochord) is membranous, composed of a cellular connective tissue which is distended with fluid to render this structure resistant to pressure. Later, the notochord becomes cartilaginous, to be replaced in higher forms by a vertebral column and skeleton composed nearly entirely of bone (Darwin,¹ Lull²). This transition from connective tissue to cartilage to bone in vertebrate evolution also represents the method by which the human skeleton is formed in the embryo; in addition, this same transition or series of developmental steps is seen in the majority of benign and malignant tumors of bone which are here designated as tumors of the fibrocartilaginous group (fig. 1).

In the present study, over 500 tumors of the skeleton included in this grouping are analyzed, and in their histogenesis it will be shown that these growths repeat, in a concise way, both the evolutionary development and the embryology of this type of tissue. These tumors include the osteochondromas or benign exostoses, the chondromas or chondromyxomas and the chondromyxosarcomas, the latter being a form of osteogenic sarcoma containing cartilage. Taken broadly, these three groups of lesions represent different stages of the same pathologic process and may be graded from the more primitive and malignant to the more highly differentiated and benign—the most primitive, the chondromyxosarcoma, being malignant, the chondromas being potentially malig-

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* Illustrations by Mr. Herman Schapiro.

* From the Surgical Pathological Laboratory, Johns Hopkins Hospital and University.

1. Darwin, C.: *Origin of the Species*, ed. 1, London, J. Murray, 1859.

2. Lull, R. S.: *Organic Evolution*, New York, The Macmillan Company, 1927, p. 460.

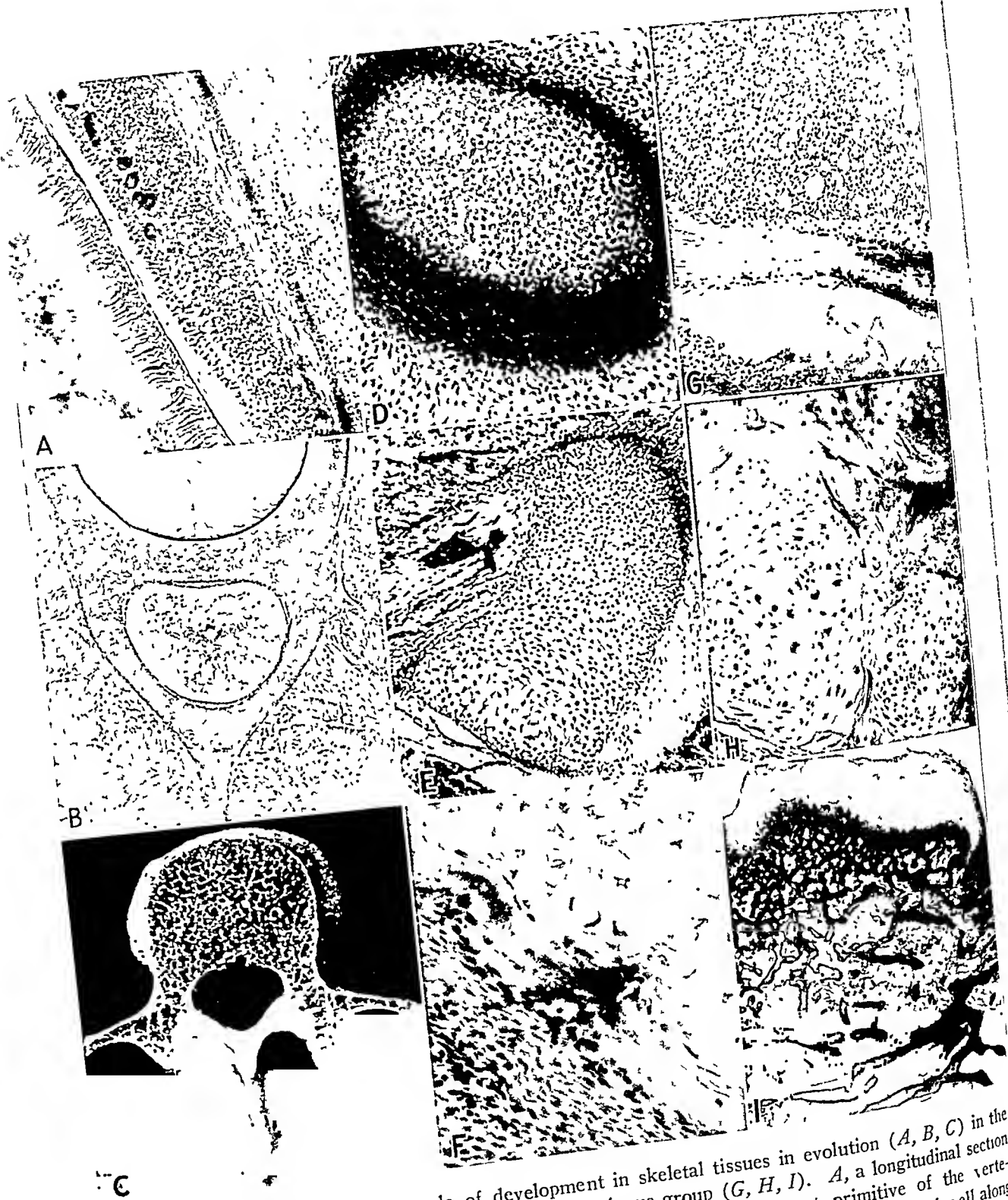


Fig. 1.—Comparison of the cycle of development in skeletal tissues in evolution (A, B, C) in the embryo (D, E, F) and in tumors of the fibrocartilaginous group (G, H, I). A, a longitudinal section of the membranous spine or notochord of the amphioxus, one of the most primitive of the vertebrates; B, the essentially cartilaginous structure of the vertebrae in the dog fish, an animal well along in the scale of evolution of the vertebrates; C, the osseous structure of the adult vertebrae in man; D, the first step in the formation of the skeleton in the human embryo, with primitive connective tissue or mesenchyme condensing at the site of the future vertebrae; E, the early formation of cartilage about calcified cartilage which is being resorbed by giant cells, one of which is shown in the picture. This is the final stage of ossification on the human embryo. G shows the microscopic appearance of a chondromyxosarcoma at the margin of the tumor. The neoplastic tissue is a proliferation of embryonic connective tissue and fetal cartilage cells or so-called myxoma. H shows the essentially cartilaginous structure of a benign chondroma, and I, the predominantly osseous structure of a benign osteochondroma.

nant in their recurrent form and the osteochondromas being essentially benign. Histologically also, there is no sharp dividing line between these three forms of neoplasms, since the basic tissues comprising them, connective tissue, cartilage and bone, are present in varying amounts in all of these growths.

OSTEOCHONDROMAS

The osteochondromas, or exostoses, are benign tumors, usually occurring in persons between the ages of 10 and 25 years near the end of the long bones and forming bony skeletal outgrowths with a thin cartilaginous cap. The symptoms are generally mild and of long duration, averaging over five years. The roentgenogram of the involved bone gives a typical picture in which the characteristic features are a base or pedicle, springing directly from the cortex of the underlying bone without an intervening zone of abnormal osseous tissue and with an overlying expanding cap composed of cartilage undergoing calcification or ossification. Microscopic examination of the excised tumor reveals normal laminated bone beneath a transitional zone of calcifying cartilage which is overlayed by a thin strand of fibrous tissue. Histogenetically, it will be shown, these tumors are an exaggeration of a normal bony protuberance intended for the anchoring of an important tendon.

CLINICAL FEATURES

While the roentgenogram and the microscopic section of an osteochondroma usually present fairly uniform changes, many of the clinical features of this lesion are notably variable. This type of skeletal outgrowth which is generally contiguous with the bone, but which rarely may be entirely separated from it and embedded in the substance of a tendon or of a soft part structure, is associated with many different etiologic factors. Some of these tumors are undoubtedly congenital; in addition, there is a distinct familial history. Cases in which several members of the same family in one or more generations are affected by multiple outgrowths of the exostosis type are by no means rare (Ehrenfried³). At the opposite extreme, development of a type of tumor identical in histologic structure with such congenital exostoses may take place in adult life as the result of chronic infection, the calcaneal spurs in chronic gonorrheal arthritis being a common example.

This variability of etiologic factors is reflected in the age incidence of the disease, for while osteochondromas are essentially a neoplasm of the early decades with the peak of the curve of age incidence between 10 and 20 years, about 30 per cent are observed in patients over 30

3. Ehrenfried, A.: Hereditary Deforming Chondrodysplasia; Multiple Cartilaginous Exostoses: A Review of the American Literature and Report of Twelve Cases, *J. A. M. A.* **68**:502 (Feb. 17) 1917.

years of age (fig. 2). Those exostoses in patients under 30 are either congenital or traumatic and rarely infectious (due to gonorrhea contracted during the postadolescent period). After the age of 30, infection plays a greater rôle in the onset of the growth, the various types of chronic arthritis being responsible for a definite group of these tumors occurring in adults. The types of exostoses occurring early in life, congenitally or traumatically, also may be recorded in patients well over 30, since the absence of symptoms often permits a latent period of over twenty-five to forty years. This tendency of osteochondromas to remain latent or

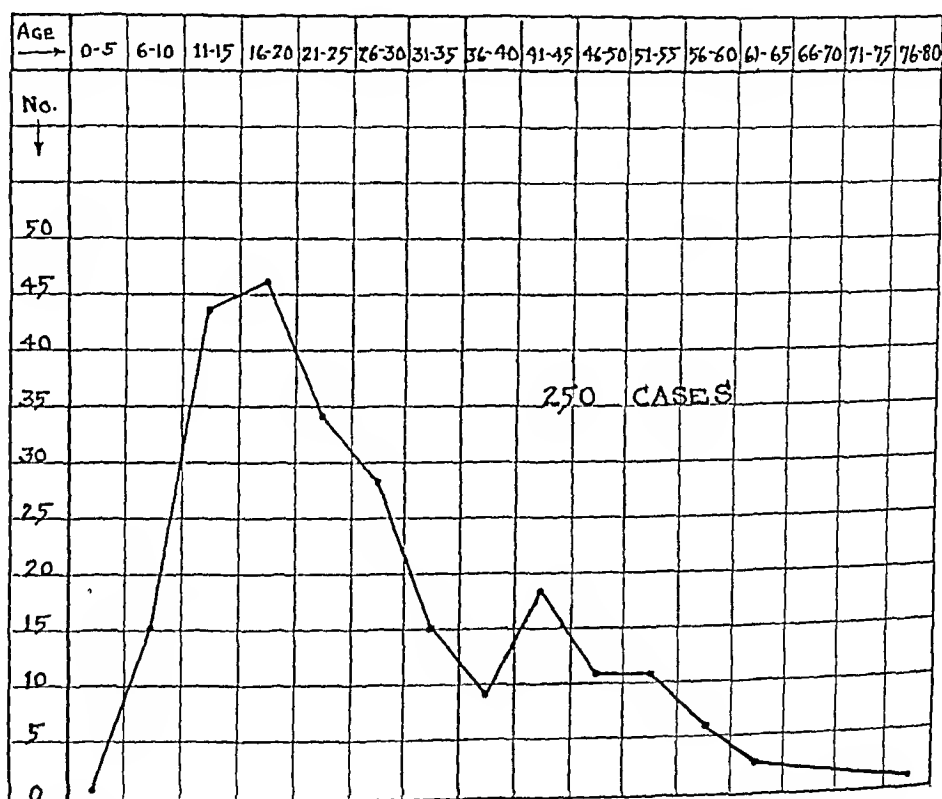


Fig. 2.—Chart showing the age incidence of benign osteochondromas, or exostoses.

evade clinical observation is shown by the fact that although 25 per cent of these lesions apparently date from birth, only 6 per cent are observed clinically in patients less than 10 years of age.

Figure 3 shows the skeletal distribution of these exostoses. In analyzing the distribution of these tumors, it was found that nearly twice as many males were affected as females and that whites predominated, only 16 colored patients being present in this series of 262 cases. Nearly one third of the tumors occurred about the knee joint in the lower end of the femur or upper end of the tibia. The majority of the remaining tumors were located at the ends of the long bones of the ankle, the shoulder, the hip or the elbow. The other sites of importance are the

region of the jaw and skull and the small bones of the foot or hand. It must be borne in mind, however, that tumors of the skull and jaws often grouped under exostoses are, properly speaking, osteomas, representing a different type of ossification in fibrous tissue, and that some of the tumors of the small bones of the hand and feet either fall into this category or are related to aberrant sesamoid bones.

The striking feature of the skeletal distribution of osteochondromas is their periarticular location and their relation to sites of tendinous

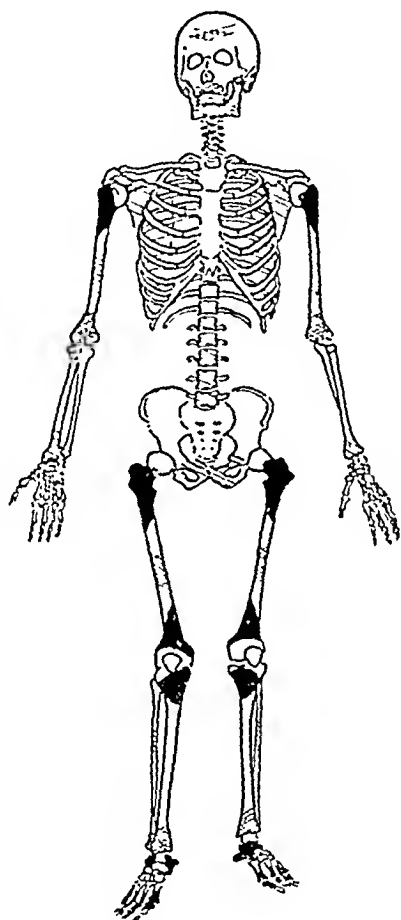


Fig. 3.—Incidence of osteochondroma according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites; the diagonal lines, the occasional or rare locations.

attachments. These tendons are generally those involved in regions of maximal traction, being at the ends of such muscles as the adductor magnus and quadriceps femoris in the thigh and the gastrocnemius and soleus at their convergence in the Achilles tendon. A further peculiarity of these sites is the fact that the tendons attach not to the periosteum but directly to the bone.

The average duration of symptoms for the cases of osteochondroma listed in table 1 is sixty-one months, or slightly over five years. This

TABLE 1.—Benign Osteochondromas (Exostoses)

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
44019*	C	M	18	Tibia, left	4	Pain; tumor	Multiple pedicle exostoses	Excision, Jan. 21, 1929	New bone	Discharged well
44257	W	F	45	Femur, external condyle	..	Fracture; pain	Excision, November, 1923	Cancellous bone; old cartilage	Discharged well
43691	W	F	56	Toe	72	Bursa over exostosis with cartilagin-	Removal of toe	Discharged well
43549	W	M	16	Tibial tuberosity	72	Trauma; pain; tumor	Excision	Cancellous bone; adult cartilage	Discharged well
43497	W	M	14	Femur, lower right	12	Trauma; pain; tumor	Excision, June, 1923	Cancellous bone; adult cartilage; some fetal cartilage	21 mo. well
43347	W	M	18	Toe, left	Excision, May, 1923	Cancellous bone; old cartilage	Discharged well
43185	W	M	40	Thumb, left	Rounded exostosis	Excision, March, 1923	Cancellous bone; adult cartilage; some new bone	Discharged well
43095	C	F	22	Jaw, lower	96	Tumor; deformity of mouth	Excision, March, 1923	Cancellous bone; old cartilage	Discharged well
43042	W	M	20	Fibula	..	Pain; tumor	Broad exostosis; cartilaginous cap	Excision, June, 1920	Calcifying cartilage; osteoid tissue
42797	W	F	18	Skull, frontal	144	Trauma; tumor	Rounded exostosis	Excision, February, 1923	Cancellous bone	Discharged well
42142	W	M	11	Tibia, upper, left	..	Tumor	Cystic periosteal shadow
41825	W	M	19	Foot, dorsum	48	Trauma; pain; tumor	Rounded exostosis over joint	Excision, Aug. 1, 1927	Cancellous bone; adult cartilage	Discharged well
41563	W	M	18	Femur	Excision, June 24, 1927	Cancellous bone; adult cartilage	Discharged well
41519	W	F	15	Toe, right foot	Excision, June 18, 1927	Cancellous bone	23 mo. well
41267	W	M	39	Femur and tibia	Excision, May 2, 1927	Cancellous bone, adult and calcified cartilage	Discharged well
41260	W	F	62	Foot, second metacarpal	2	Trauma; pain	Bone formation with transverse fracture	Blopsy	Cancellous bone	1 yr. well
40896	W	M	13	Tibia, lower end	9	Trauma; pain; tumor	Rounded exostosis
40702	W	F	9	Humerus, upper end	5	Rounded exostosis, cystic	No operation	20 mo. well
40652	W	M	20	Fibula and tibia	96	Tumor	Rounded exostosis, cystic	No operation
40648	W	M	..	Humerus, upper	9	Tumor	Cystic periosteal shadow	No operation	Well 29 mo.
40545†	W	M	15	Femora, multiple	180	Congenital tumors; abnormal gait	Excision, January, 1927	Cancellous bone; calcified cartilage	Discharged improved
40523	W	M	20	Humerus	..	Tumor	Excision, January, 1927	Cancellous bone; adult cartilage	Discharged well

40352	W	F	40	Femur, lower end	Excision, March, 1928	..	1 mo. well
40250	W	M	50	Femur, lower third	420	Trauma; tumor	Pedicle exostosis	Excision	..	2 yr. well
40071	W	F	..	Toe, left foot	Excision, October, 1926	..	Discharged well
40040	W	M	14	Femur, interior shaft	24	Tumor	Pedicle exostosis	Excision, Jan. 24, 1928	..	2 yr. well
39835	..	M	43	Palate, hard	Excision	..	Discharged well
39916	W	F	11	Humerus, upper third	24	Pain; tumor	Pedicle exostosis	No operation	..	2½ yr. well
39782	W	F	6?	Radius, lower	60	Tumor	Pedicle exostosis	No operation	..	2 yr., condition unchanged
39502	W	F	11	Femur, lower	1	Tumor	Broad exostosis; cartilaginous cap	Excision, July, 1927	..	2½ yr. well
39472	W	M	19	Femur, lower	120	Tumor	Broad exostosis; cartilaginous cap	Excision	..	2½ yr. well
39445	W	M	41	Neum, lip, right, acetabulum	36	Pain; tumor	..	Excision, June 9, 1926	..	Discharged well
39443	W	F	56	Femur, right, internal condyle	Excision, June, 1926	..	3½ yr. well
39421	W	M	45	Maxilla, right	18	Tumor	Obliteration of antrum	Excision, June, 1926	..	Discharged well
39405	W	F	35	Maxilla, right	Excision, June, 1926	..	Discharged well
39173	W	F	16	Femur, left	Excision, April, 1926	..	Discharged well
39064	W	F	30	Femur, upper, left	18	Pain; tumor	Cauliflower exostosis	None	..	Discharged well
38845	W	F	55	Jaw	Rounded exostosis	Excision, March, 1926	..	Discharged well
38784	W	F	10?	Scapula, right	6	Tumor	Pedicle exostosis	Excision	..	2½ yr. well
38780	W	M	45	Femur, lower	Pedicle exostosis	Well, 1929
38694	W	F	..	Tibula, upper	Broad exostosis; cartilaginous cap	Well, 1928; lost
38613*	W	M	28	Femur, right; fifth lumbar vertebra	96	Trauma; pain; tumor	..	Excision, 1926, 1928	..	2 yr. well
38466	W	M	23	Os calcis	Pedicle exostosis in achilles' tendon	Excision, 1923	..	Well, 1929
38460	W	M	12	Humerus, upper	¼	Tumor	Broad exostosis; cartilaginous cap	Discharged well
38215	W	F	40	Jaw, left, lower	Excision, November, 1925	..	Discharged well
37582	W	F	18	Humerus, shaft	4	Tumor; pain	Broad exostosis; cartilaginous cap	Excision, February 1926	..	4 yr. well
37540*	W	F	30	Humerus, left upper tibia, fibula, right	252	Tumor	..	Excision, 1925	..	Discharged well
37373	W	M	18	Humerus, upper, right	6	Trauma; tumor	Broad exostosis	Excision, May, 1925
37365	..	F	31	Toe, right, little	12	Tumor	..	Excision, May, 1925	..	Discharged well
37262	W	F	20	Tibia, lower	½	Pain	Broad exostosis; cartilaginous cap	Excision, November, 1925	..	Discharged well

* Cases of multiple exostoses.

† Cases with typical hereditary, deforming chondrodysplasia in which more than one member of the family was affected.

‡ The results of treatment shown have been figured from the date of the first operation.

TABLE 1.—Benign Osteochondromas (Exostoses)—Continued

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
37158*	W	M	21	Tibia, upper; upper right and left fibula	Multiple pedicle exostosis	Discharged well
36752	W	F	14	Fibula, left, upper	8	Pain	Broad exostosis; cartilaginous cap	Excision, manipulation, July, 1923	Cancellous bone	5 yr. well
36666	C	M	42	Knee, left	6	Trauma; pain; tumor	Hypertrophic arthritis	Excision	..	Lost
36642	W	M	12	Jaw, lower left	3	Tumor; pain	..	Excision	..	5 yr. well
36521	W	F	39	Skull, right and frontal	48	Tumor	Rounded exostosis	Excision, December, 1921	Cancellous bone; dense fibrous tissue	5 yr.; no recurrence
36402*	..	M	9	Tibia, shaft; femur, upper and lower	12	Bowing; slight trauma	Metaphyses widened and deformed	Straightening fracture
36189	16	Arm	..	Trauma	Pedicle exostosis; cartilaginous cap	Excision
35867	W	F	11	Humerus, right	48	Tumor	..	Excision	Cancellous bone; old cartilage	Discharged well
35881	W	F	15	Toe, right, middle	Excision	Cancellous bone; old cartilage	5½ yr. well
35826	W	M	33	Tibia, internal condyle	60	Tumor; pain	Broad exostosis	..	Cancellous bone beneath normal nail-bed	6½ yr. well
35760	W	M	29	Femur, lower, left	6	Trauma	Broad exostosis; cartilaginous cap	Excision	Fibrous tissue	Discharged well
35720	W	M	15	Tibia, upper	24	Trauma; tumor	Pedicle type with bursa	Excision	Cancellous bone; adult cartilage	Well over 1 yr.
35718	W	F	15	Femur, shaft	12	Tumor	Broad exostosis; cartilaginous cap
35714	W	M	10	Femur, shaft, lower third	48	Trauma; tumor	Pedicle exostosis; cartilaginous cap	Excision	Cancellous bone; adult cartilage; many giant cells	Discharged well
35712	W	F	16	Tibia, shaft, left	48	Tumor	Broad exostosis; cartilaginous cap	5½ yr. well
35661	W	M	24	Toe, large left; distal phalanx	168	Tumor	..	Excision, June, 1921	Cancellous bone; fetal adult and calcified cartilage	Discharged well
35624*	..	M	..	Fibula, upper; tibia, upper	..	Tumor; pain	Metaphyses widened and deformed	Lost
35382*	W	M	19	Tibia, upper and lower; fibula; ulna	48	Tumors; multiple	Multiple pedicle exostosis; metaphyses widened
35380	..	M	..	Femur, left lower	36	Trauma	Broad exostosis; cartilaginous cap	5½ yr. well
35366	W	F	18	Tibia, left, lower external	24	Tumor; pain	Broad exostosis; cartilaginous cap	Excision, June, 1921	..	5½ yr. well
35237	W	M	21	Os calcis, right	Excision, April, 1921	..	Discharged well
35108	..	F	5	Temporal bone	Area of bone destruction under rounded exostosis	..	Cancellous bone	6 yr. well

35010	W	M	23	Radius, upper, right	6	Pain	Cystic tumor	Curettement, 1924	6 yr. well
34605	W	F	46	Os calcis, left	12	Tumor; pain	Excision, February, 1924	Cancellous bone; adult cartilage	6 yr. well
34436	W	M	17	Femur, shaft	2	Trauma	Flat, broad, ossifying perostitis	Not advised
34244	W	M	50	Auditory canal, external	10	Tumor	Discharged well
34167	W	M	39	Os calcis	Operation, October, 1923	Cancellous bone; adult cartilage
33986	W	F	23	Skull, right	172	Tumor; pain	Rounded exostosis	No operation	5½ yr. well
33944	W	M	12	Tibia, left, upper	15	Tumor	Pedicle exostosis; cartilaginous cap	Excision, August, 1924	Cancellous bone
33926	W	M	..	Humerus, external condyle	..	Tumor	Rounded exostosis	Excision, September, 1923	Cancellous bone; adult cartilage	Discharged well
33750	W	F	18	Femur, lower	24	Trauma; tumor	Broad exostosis; cartilaginous cap	No operation
33553	W	M	19	Humerus, mid-shaft, right	228	Congenital tumor	Periosteal cauliflower mass	Excision, August, 1922	Adult cartilage; cancellous bone	Well 7 yr.
33168	W	M	13	Humerus, upper, right	..	Tumor; fracture	Fracture through pedicle exostosis	Excision ?	6½ yr. well
33155	W	M	30	Femur, lower, right	24	Tumor; trauma; pain	Pedicle exostosis; cartilaginous cap	Excision, 1915, 1923	Calcified cartilage; adult cartilage; myxoma	Recurred; well, 1924
32889	W	M	30	Pubis	..	Trauma; tumor	Rounded exostosis	Adult cartilage	Well 7 yr.
32601	W	M	44	Scapula	18	Pain	Periosteal translucent area; rarefaction beneath	Exploration, April, 1923
32515	W	M	43	Pubis, left	4	Trauma; tumor	Broad exostosis; cartilaginous cap	No operation	Tumor larger, 7 yr.
32508	W	M	22	Femur, lower, right	36	Trauma; tumor; pain; limping	Rounded exostosis	Lost
32494	W	F	56	Ulna, styloid	72	Tumor	Sesamoid bone ?	Operation refused	7 yr. well
32357	W	M	13	Skull	..	Tumor	Rounded exostosis	Excision, February, 1923	Discharged well
32317	W	M	25	Femur, shaft, right	18	Trauma; tumor; pain	Large periosteal calcifying mass	Exploration, January, 1923	Adult cartilage; cancellous bone	Well 3 mo.
32267	W	M	62	Femur, shaft	..	Pain; stiffness	Pedicle exostosis	No operation	7 yr. well
32030	W	F	46	Femur, lower	192	Trauma; tumor; pain	First, ossifying tumor; second, osteophytes in stump	Amputation, 1916; disarticulation, 1923	New bone; adult cartilage	Recurred; well, 1926
31682	W	M	6	Humerus, upper, left	..	Tumor	Broad exostosis	Biopsy, 1923	Hyaline cartilage and cancellous bone	Well 5 yr.
31594	W	F	28	Humerus, upper	144	Trauma; tumor	Large periosteal translucent area	Cauterized, 1922; excised, 1924	Cancellous bone; adult cartilage	Well 6 yr.
31522	W	F	14	Femur, lower	36	Trauma; tumor	Pedicle exostosis; cartilaginous cap	Exploration	Cancellous bone	6 yr. well
31132	W	M	17	Femur, lower, right	16	Tumor; pain	Pedicle exostosis	Well 8 yr. after onset
31064	W	M	16	Femur, lower, right	12	Tumor	Pedicle exostosis

TABLE 1.—*Benign Osteochondromas (Exostoses)*—Continued

Pathologic No.	Race	Sex	Age	Location	Dura- tion, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
30090	W	M	30	Metatarsals, fourth and fifth, right	180	Trauma; tumor; pain	Rounded exostosis	Excision, June, 1922	Cancellous bone	Discharged well
30568*	W	F	28	Femur; tibia; fibula	192	Tumor; tenderness	Multiple pedicle exostosis	Excision	Cancellous bone; adult cartilage	Well over 7 yr.
30453	W	M	18	Tibia, upper, left	..	Pain	Pedicle exostosis	Excision
30452	W	M	24	Femur, lower, right	72	Trauma; tumor	Pedicle exostosis
30451	W	M	24	Femur, lower, right	60	Tumor	Broad exostosis
30450	W	M	19	Femur, lower, right	18	Trauma; pain; stiff- ness; familial	Pedicle exostosis
30449	W	M	21	Femur, lower, right	..	Pain; tumor	Pedicle exostosis
30436	W	M	30	Humerus, lower, left	..	Tumor	Pedicle exostosis	Incised, March, 1922	7 yr. well
30398*	W	M	..	Frontal bone, right; clavicle, right; maxilla, left	..	Syphilitic history	Multiple rounded exostosis	Antisyphilitic, 1922	Exostosis dis- appeared
30393	W	F	34	Occiput	12	Tumor	Broad exostosis	Unchanged 6 mo.
30304	..	M	..	Femur; tro- chanter; left	42	Pain	Excision, February 1922	Cancellous bone; adult cartilage	Discharged well
30265	W	M	16	Second metatar- sal, right	1½	Tumor	Excision, May, 1922	Discharged well
30186	W	M	40	Femur, upper	..	Tumor	Amputation, October, 1917	Well 5 yr.
30183	W	M	11	Humerus, upper, left	1½	Tumor	Rounded exostosis	Resection, June, 1919	Well over 10 yr.
30173	W	M	15	Lumbar, first	24	Pain	Perosteal transi- ent area	Excision, September, 1915	Cancellous bone; adult cartilage	Well 11½ yr.
30120	W	F	80	Scapula	3	Pain; limitation of motion	8 yr. well
30109	W	M	37	Humerus, greater tuberosity	36	Pain; limitation of motion	Broad exostosis	No operation	Condition un- changed
30015	W	M	18	Humerus, upper, left	..	Tumor	Broad exostosis	Excision, March, 1922	Discharged well
29832	B	M	..	Humerus, lower, left	..	Tumor	Excision, March, 1922	Discharged well
29747	W	M	21	Ulna, lower	144	Tumor; limitation of motion	Excision, April, 1922	Discharged well
29661	W	M	..	Femur, neck, left	36	Trauma; pain; limi- tation of motion	Broad fuzzy exos- tosis	Excision, 1921; 1922	Cancellous bone; adult cartilage	Discharged well
29638	O	M	30	Femur, neck	36	Trauma; pain; stiffness	Recurred, well 9 yr.
29455	W	F	54	Index finger, right terminal phalanx	..	Trauma; pain	Rounded exostosis	Lost
29154*	W	F	30	Tibia; fibula; humerus	..	Tumors	Multiple pedicle exostosis	Excision, January, 1922	8 yr. well
								No operation	Unchanged 8 yr.

29009	W	16	Femur, upper	36	Trauma; tumor	Broad exostosis	Excision, September, 1921	Cancellous bone; adult cartilage	Well almost 9 yr.
28992	W	33	Femur, lower, right	48	Trauma; pain; adductor spasm	Broad fuzzy exostosis	Excision, September, 1921	Cancellous bone; adult cartilage	Well almost 8 yr.
28865	W	12	Tibia, upper	36	Trauma; tumor	Broad exostosis; cartilaginous cap	Excision, September, 1921	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Well 9 mo.
28701	W	11	Tibia, lower, right	..	Tumor	Broad exostosis; cartilaginous cap	Excision, September, 1921	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Well 9 mo.
28665	C	18	Femur	..	Tumor	Pedicle exostosis	Excision, August, 1921	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Discharged well
28601	W	36	Femur, shaft	312	Trauma; tumor	Pedicle exostosis	No operation	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Condition unchanged
28596	O	50	Humerus, right	..	Tumor	Multiple broad exostosis	Excision, July, 1921	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Discharged well
28539†	W	9	Femur, lower and upper; fibula	..	Tumors	Multiple broad exostosis	No operation	Cancellous bone; adult and fetal cartilage; myxoma in tendon	Unchanged 9 yr.
28225	W	20	Skull, frontal	228	Trauma; tumor; pain; strabismus	Rounded exostosis	Excision, May, 1921	Cancellous and new bone	Well 1 yr.
28062	W	11	Humerus, upper	36	Tumor	Broad exostosis; cartilaginous cap	Excision, 1921	Cancellous bone	Well 3 yr.
27937	W	11	Clavicle	12	Trauma; tumor	Rounded exostosis	Resection, May, 1910	Cancellous bone	Well almost 20 yr.
27816	W	23	Humerus, upper, right	24	Tumor; pain	Rounded exostosis	No operation	Cancellous bone	Condition unchanged
27697	W	23	Femur, lower	240	Trauma; tumor	Pedicle exostosis	No operation	Cancellous bone	Condition unchanged
27503	W	18	Humerus, shaft	42	Trauma; tumor; pain	Pedicle exostosis	Excision, 1920	Cancellous bone; adult cartilage	Well 6 yr.
27228	W	..	Phalanx, second	..	Tumor	Rounded exostosis	No operation	Cancellous bone; adult cartilage	Condition unchanged
27218	C	23	Os calcis	..	Gonorrheal arthritis	Calcaneal spurs	Excision, 1920	Cancellous bone; adult cartilage	Condition unchanged
27194	W	10	Femur, left	..	Tumor	Calcaneal spurs	Excision, 1920	Cancellous bone; adult cartilage	Discharged well
27157	W	11	Fibula, head	..	Tumor	Calcaneal spurs	Excision, December 1920	Cancellous bone; adult cartilage	Discharged well
27079	W	19	Ilium	6	Tumor; pain	Fuzzy broad exostosis	Excision, November, 1920	Cancellous bone; adult cartilage	1 yr. well
27051	C	17	Tibia tuberosity	36	Trauma; pain	Broad exostosis	Excision, April, 1910	New bone	20 yr. well
26781*	W	11	Radius, lower; humerus, upper	132	Tumors	Multiple pedicle exostosis	Excision, November, 1920	Cancellous bone	Discharged well
26738	W	28	Skull, frontal	276	Trauma; tumor; pain	Rounded exostosis	No operation	Cancellous bone	Condition unchanged
26656	W	21	Navicular, right wrist	4	Trauma; tumor; pain	Multiple pedicle exostosis	Excision, 1912; 1914; 1920	Cancellous bone	Repeated recurrences
26610†	W	10	Multiple	..	Tumors	Multiple pedicle exostosis	Excision, August, 1920	Cancellous bone; adult and calcifying cartilage	9½ yr. well
26583	W	19	Mastoid	36	Tumor; pain; deafness	Multiple pedicle exostosis	Biopsy	Cancellous bone; adult and calcifying cartilage	Condition unchanged
26423	W	33	Skull, frontal	84	Trauma; tumor	Multiple pedicle exostosis	Excision, August, 1920	Cancellous bone; cellular fibrous tissue	Well almost 10 yr.
26392	W	14	Fibula, upper, right	36	Tumor; pain	Multiple pedicle exostosis	Excision, July, 1920	New bone; fibrous tissue	Well 1 yr.
26285	W	19	Femur, lower	48	Tumor	Pedicle exostosis	Excision, July, 1920	Cancellous bone; fetal and adult cartilage; myxoma	Discharged well
26285	W	19	Femur, lower	48	Tumor	Pedicle exostosis	Excision, 1910; 1920	Cancellous and new bone	Recurrence, well 10 yr. after second operation

TABLE 1.—*Benign Osteochondromas (Exostoses)*—Continued

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
20272	W	F	55	Humerus, right	36	Trauma; pain; stiffness	Excision, June, 1920	Cancellous bone	Well 9½ yr.
26120	W	F	59	Femur, upper, right	300	Infection	Excision, May, 1920	Cancellous bone
26097	W	M	51	Femur, upper, right	..	Tumor	Excision, 1920	Cancellous bone and adult cartilage	Discharged well
26059	W	F	47	Astragalus, right	..	Tumor	Excision	Cancellous bone and adult cartilage	Walking almost impossible after 10 yr.
25955	W	M	10	Os calcis	14	Pain	Rounded exostosis	Excision	Cancellous bone and adult cartilage	Discharged well
25852	W	M	49	Radius, head	..	Tumor	Excision, March, 1920	Cancellous bone and adult cartilage	Discharged well
25802	W	M	11	Third lumbar vertebra, transverse process	27	Pain; tumor; stiffness	Excision, March, 1920	Cancellous bone and adult cartilage	Discharged well
25432*	W	F	13	Humeri; fingers; tibiae	132	Multiple tumors	Multiple pedicle and broad exostosis	No operation	Condition unchanged
25128	W	M	47	Fifth lumbar vertebra	12	Pain on standing	Excision, October, 1919	Cancellous bone	Well 10 yr.
24938	W	M	19	Tibia tuberosity	24	Tumor	Expanded, rarefied, subcuticular area
24432	W	M	12	Tibia, upper	24	Tumor; pain	Fracture through exostosis	Excision, April, 1919	Adult and enflekying cartilage	Discharged well
24212	W	F	19	Navicular, left foot	33	Fracture; tumor; pain	Calcaneal spurs
24014	W	M	32	Os calcis	48	Gonorrheal arthritis; pain	Overgrowth in Albee transplant	Excision, January, 1919	Cancellous bone in tendon	Discharged well
24003	W	F	24	Spine	48	Pain	Pedicle exostosis	Excision, May, 1922	Cancellous bone in tendon	Discharged well
23886	W	M	30	Phalanx, little finger	..	Tumor	Broad exostosis	Excision, 1918	Cancellous bone; adult cartilage	Well 1 yr.
23885	W	M	21	Tibia, upper	72	Tumor	Broad exostosis	Excision, December, 1916	Cancellous bone; adult cartilage	Well 5 yr.
23767	W	M	45	Femur, neck	24	Pain; limitation of motion; gonorrheal history	Broad exostosis	Excision, November, 1918	Cancellous bone; enflekying cartilage	Discharged well
23799	W	F	27	Spine	12	Purpura	Excision, 1918; 1925	New bone	Died, 1926; decubitus ulcers
23583	W	M	16	Humerus, lower	14	Fracture; tumor; limitation of motion	Exuberant callus	Excision, August, 1918	Cancellous bone	Discharged well
23428	W	M	26	Big toe, right	60	Trauma; tumor	Broad exostosis	Excision, July, 1918	Lost
23205	W	F	10?	Humerus	..	Tumor	Excision, July, 1918
23207	W	F	43	Femur, left head	8	Pain; limitation of motion	Excision, March, 1919	Cancellous bone in tendon	Well almost 21 yr.
23227	W	M	23	Os calcis, left	3	Gonorrheal arthritis	Calcaneal spur	Excision, February, 1917	Cancellous bone; enflekying cartilage in tendon	Discharged well

22733	W	M	19	Os calcis	..	Pain	Calcaneal spur	Excision, January, 1918	Calcified cartilage in tendon, myxoma	12 yr. well
22806	W	M	7	Humerus, shaft	60	Tumor; pain; limitation of motion	Excision, October, 1927	Cancellous bone; adult	Well 4 yr.
22070	W	M	25	Femur, lower, left	240	Tumor	Multiple rounded exostosis	No operation	Well 11 yr.
22005	W	M	25	Os calcis	..	Gonorrheal arthritis	Calcaneal spurs	Excision, August, 1917	Cancellous bone and calcified bone in tendon	Discharged well
21915	W	M	..	Humerus	..	Tumor	Excision, July, 1917	Cancellous bone; adult	Well over 12 yr.
21080	W	M	34	Os calcis	60	Gonorrheal arthritis	Calcaneal spurs	Excision, June, 1917	Cancellous bone and cartilage in tendon	Reurred, arthritis
21482	W	M	..	Femur, upper	.	Fracture; exuberant calus	Excision, February, 1917	Cancellous bone; adult	Discharged well
31424	W	M	..	Fifth lumbar vertebra	..	Pain; tumor	Excision, April, 1917	Cancellous bone; adult	Discharged well
21208	W	F	15	Femur, lower, left	24	Tumor	Pedicle exostosis	Excision, March, 1917	Cancellous bone; adult	Well 13 yr.
20881	W	M	..	Os calcis	..	Tumor; pain	Calcaneal spurs	Excision, January, 1917	Cancellous bone	Well 2 yr.
20787	W	M	..	Os calcis	..	Pain	Calcaneal spurs	Excision, January, 1917	Cancellous bone; adult	Dead other causes
20803	W	M	..	Os calcis	..	Pain	Calcaneal spurs	Excision, October, 1916	Cancellous bone; adult	Discharged well
20182½	W	F	6	Humerus, right; femur; left; ankle; wrist	60	Tumors	Multiple pedicle exostosis	No operation	Unchanged 6 yr.
20156	W	M	..	Os calcis	4	Pain	Calcaneal spurs	Excision, September, 1916	Cancellous bone; cartilage, myxoma	Well over 18 yr.
18751	W	M	51	Vertebra, ninth dorsal	12	Pain	Excision, 1915; 1916	Cancellous bone; adult	Dead, second operation
18607	W	M	28	Os calcis	48	Gonorrheal arthritis	Calcaneal spurs	Excision, December, 1915	Cancellous bone	Arthritis recurred 6 yr. later
18387	W	F	..	Skull	..	Tumors	Excision, 1915; 1916	Cancellous bone	Reurred
18505	W	M	33	Fibula, head	1	Tumor	Broad exostosis	Resection, October, 1915	Cancellous bone	Well over 14 yr.
17987	W	M	16	Femur, left	..	Tumor	Excision, April, 1915	7 yr. well
17003	W	F	51	Tumor	Excision, February, 1915	Cancellous bone; adult	No improvement 7 yr.
16935	W	F	27	Femur, lower, right	60	Stiffness; pain	Fracture through pedicle exostosis	Excision, December, 1914	Cancellous bone; adult	Discharged well
16862	W	M	30	Os calcis	..	Pain	Calcaneal spurs	Excision, December, 1914	Cancellous bone; adult	8 yr. well
16621	W	M	13	Humerus, left	48	Tumor	Excision, December, 1914	Cancellous bone; adult	Discharged well
16491	W	M	18	Big toe, right	..	Tumors	Excision, November, 1914	Cancellous bone; adult	Discharged well
16120	W	M	..	Fibula, upper	..	Tumor after typhoid fever	Broad exostosis	No operation
16286	W	M	..	Femur	84	Tumor; pain	Excision, September, 1914	Cancellous bone; adult	Discharged well
16273	W	M	31	Astragalus	..	Tumor	Cancellous bone; adult	Discharged well

TABLE 1.—*Benign Osteochondromas (Exostoses)*—Continued

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
15032	W	M	48	Foot, right	72	Tumor	Excision, June, 1914	Discharged well
15010	W	M	39	Tibia, upper	24	Tumor	Excision, 1914	Adult cartilage; new bone	Well 7 yr.; suicide
15003	W	F	20	Toe	36	Tumor	Excision, May, 1914	Cancellous bone; adult cartilage	6 yr. well
15335	W	M	15	Femur, lower, right	72	Tumor	Broad exostosis	Excision, March, 1914	Cancellous bone; adult cartilage	2 yr. well
15203*	W	M	31	Both feet	144	Pain	Excision, January, 1914	Cancellous bone; adult cartilage	Discharged well
15022	W	M	45	Scapula, right	1	Pain and muscle atrophy	Excision, December, 1913	Cancellous bone in tendon	Well over 16 yr.
14863*	W	M	34	Second and third lumbar vertebra	12	Pain	Excision, November, 1913	Dead
14937	O	F	33	Lower jaw	48	Tumor	Excision, November, 1913	Cancellous bone	Discharged well
14744	W	M	15	Femur, lower, right	60	Tumor; pain	Pedicle exostosis	Excision, October, 1913	Cancellous bone; adult cartilage	Discharged well
14671	W	M	29	Os calcis	14	Trauma; tumor	Excision, September, 1913	Cancellous bone; fetal cartilage	Well 6 yr., lost
14590	W	F	54	Radius, lower, right	3	Pain; tumor	Excision, August, 1913	Cancellous bone	Well 9 yr.
14342	W	M	42	Os calcis	84	Pain	Excision, 1913; 1916	Cancellous bone; cartilage, myxoma	Improved 5 yr. after recurrence
14331	W	M	15	Fibula, lower, left	3	Trauma; tumor; pain	Excision, June, 1913	Cancellous bone; calcifying cartilage	Well 6 yr.
14249*	W	M	15	Fingers, both hands	156	Tumor; pain	Excision, June, 1913	Adult cartilage	Well over 16 yr.
14175	W	M	22	Femur, lower, right	3	Tumor	Pedicle exostosis	Excision, May, 1913	Discharged well
13803	W	M	..	Tibia, lower	24	Tumor	Pedicle exostosis	Excision, 1913	Cancellous bone; adult cartilage	Discharged well
13722	Finger	..	Tumor	Amputation, 1913	Cancellous bone; adult cartilage	Discharged well
13283	W	M	24	Os calcis	18	Pain; tumor	Excision, October, 1912	Cancellous bone; adult cartilage	Discharged well
12770	W	M	22	Humerus, upper, left	180	Tumor	Broad exostosis; cartilaginous cap	No operation	Unchanged
12493*	C	M	9	Humerus and femur	48	Multiple tumors pathologic fracture of femur	Central and peripheral changes in femur	Excision and curettage of humerus	Cartilage; no myxoma	Well 10 yr.
11957	W	F	65	Os calcis	36	Trauma; tumor	Excision, August, 1911	Cancellous bone in tendon	Well 10 yr.; died of other causes
11895	O	F	50	Skull	..	Tumor	Excision, August, 1911	Dead after 1 yr.
11891	W	M	16	Femur, lower	1	Pain	Excision, June, 1911	Well 16 yr.; died of other causes
11354	W	F	28	Femur, lower	192	Trauma; tumor	Excision, February, 1911	Discharged well

11023	W	M	42	Skull	288	Trauma	No operation	Well 11 yr.
10123	W	F	7	Metacarpal	..	Tumor	Excision, November, 1909	Cancellous bone; adult cartilage	Discharged well
9916	W	M	23	Os calcis	48	Pain	Excision, 1909	Discharged well
9890	W	F	27	Femur, lower	180	Tumor	Pedicle exostosis	Excision, August, 1909	Discharged well
9720	W	M	30	Humerus	48	Tumor	Excision, May, 1909	Cancellous bone; adult cartilage	Well 13 yr.
9675	W	M	12	Cervical spine	30	Pain	Rounded exostosis	Excision, May, 1904	New bone; fibrous tissue	Well 25 yr.
9602	W	F	27	Femur, lower	36	Tumor; pain	Excision, March, 1909	Discharged well
9029	O	M	23	Femur, lower	24	Tumor; limitation of motion	Pedicle exostosis	Excision, June, 1908	Cancellous bone; adult cartilage	Discharged well
7881	W	M	24	Femur, lower	8	Trauma; pain; tumor	Excision, January, 1907	Cancellous bone; adult cartilage	Well 23 yr.
6315	W	F	40	Humerus, upper, right	4	Tumor	Pedicle exostosis	Excision, October, 1905	Well 24 yr.
6307	W	M	30	Ilium, crest	6	Tumor	Fuzzy broad exostosis	No operation	Well 12 yr.
6231	O	F	12	Femur, lower, left	36	Tumor; pain	Excision, April, 1905	Cancellous bone	Discharged well
6232	O	M	21	Femur, lower, right	144	Tumor; pain	Rounded exostosis	Excision, May, 1905	Cancellous bone; adult cartilage	Well 16 yr.
6023	W	F	..	Tibia, upper	..	Tumor
5957	O	M	24	Tibia	48	Trauma; ulcer	Excision, December, 1904	Discharged well
5813	W	M	14	Tibia, shaft	36	Tumor; pains	Excision, October, 1904	Dead other causes
5040	W	F	12	Toe, phalanx	..	Tumor	Excision, July, 1904	Discharged well
5188	W	M	24	Tibia, lower	..	Tumor	No operation	Unchanged
5520	W	F	45	Upper jaw	163	Tumor; pain	Rounded exostosis	Excision, May, 1904	Cancellous bone; fibrous tissue	Recurred 9 yr. later
5392	O	M	18	Os calcis	5	Gonorrheal arthritis	Calcaneal spurs	Excision, March, 1904	Discharged well
4112	W	M	52	Femur, shaft	228	Trauma; tumor	Excision, 1902	Well 20 yr.
3892	W	M	11	Scapula, right	48	Tumor	Excision, August, 1901	Well over 28 yr.
3746	W	F	17	Jaw, left, lower	36	Tumor	Excision, 1895
3693	W	F	54	Iscium	120	Pain	Excision, 1895	Well 3 yr. later
2914	W	F	13	Scapula, left	48	Tumor	Pedicle exostosis	Excision, 1900	Cancellous bone; adult cartilage	Discharged well
2497	W	F	15	Sternum	24	Pain	No operation	Unchanged
2071	W	M	51	Tibia, tuberosity	84	Pain	Well 9 yr. later
1632	W	M	22	Big toe	..	Tumor	Excision, 1892	Discharged well
1622*	W	M	1	Radius	1	Multiple tumors	Excision, 1892
1257	W	F	25	Femur, lower	168	Tumor; pain	Pedicle exostosis	Excision, 1891
7521	W	M	45	Scapula	60	Tumor
800	W	M	30	Humerus, upper	18	Pain; tumor	Amputation, 1894	Dead other causes 7 yr. later
743	O	F	41	Skull, frontal	98	Trauma; tumor	Excision, 1890
739	W	M	20	Jaw, lower angle	36	Tumor	Excision, 1890	Well 8 yr. later
590	W	M	33	Femur, lower	5	Trauma; tumor	Excision, 1891
502	W	F	11	Tibia, head	6	Tumor; pain	Excision, June, 1890	Well 32 yr.
410	O	F	18	Scapula	448	Tumor	Excision, 1890

duration of symptoms corresponds closely to the average time of four and one-half years computed by Meyerding⁴ in a study of 232 cases reported from the Mayo Clinic. This protracted course bespeaks benignity, for in this condition, as in most neoplasms, the longer the duration of symptoms the greater the curability of the disease.

The benign course of these lesions is further reflected in the character of the symptomatology. Pain is rarely severe, and when other than a mild ache or discomfort is present there is usually some complicating factor. Such complicating factors may take the form of bursitis or infection from irritation in the overlying soft parts, or repeated trauma may bring on such a condition in a region where swelling interferes with the use of the affected member.

More rarely, acute symptoms may follow a sudden increase in the rate of growth in the tumor. Compression of important vessels may cause edema and pain and bring the patient under observation. When such acute symptoms can be attributed to an increased growth rate in the tumor, malignant change is always to be suspected. It is a common and justifiable habit of clinicians to be influenced in favor of making the diagnosis of a benign condition when the history of the tumor extends over a number of years, as it does in most cases of exostoses. It is therefore important to call attention here to the fact that despite the duration of the disease, malignant change marked by exacerbation in the symptomatology may take place at any time in these lesions, and in such cases the most important evidence is the growth rate in the tumor and not the duration of the disease. In making a diagnosis of malignancy, it is helpful to know that the malignant change is most frequent after the age of 30 and that care must be taken to rule out an acute bursitis or inflammation in the overlying soft parts.

The location of the lesion is an important factor in leading to its discovery, although tumors in any area may be accidentally disclosed by a roentgenographic examination made for other reasons. Exostoses occurring about the pelvis are particularly prone to exist without giving any clues to their presence.

Stiffness in the adjacent joint after prolonged use of the limb is not an infrequent symptom. Apparently the stiffness or limping is brought on through irritation by the bony tumor to the overlying ligaments and tendons during the use of the limb. Rest of the affected part brings early relief from these symptoms.

Physical examination of the patient with exostosis is usually productive of only local observations. In only two instances in this series was there a positive Wassermann reaction or definite syphilitic history, and the blood and urine were uniformly negative. In a definite percentage

4. Meyerding, H. W.: Exostosis, *Radiology* 8:282 (April) 1927.

of the cases in which some systemic or hereditary factor is operative the lesions may be multiple. Arthritis associated with gonorrheal infection may be a determining factor in such instances.⁵ A familial disease known as hereditary deforming chondrodysplasia may be responsible. This last group of hereditary multiple exostoses is discussed subsequently.

Local examination of the tumor reveals a firm swelling securely attached to the underlying bone. There is little or no tenderness to be



Fig. 4 (P. N. 35720).—Roentgenogram showing a typical exostosis in the upper end of the tibia near the insertion of the quadriceps tendon. The outgrowth is continuous with the normal bone beneath and a distinct bursa overlies the exostosis. The presence of a calcareous bursitis makes this complication clearly visible.

made out on deep pressure. The soft parts overlying the tumor are most often freely movable unless there has been undue irritation with

5. While the osteophytes common to hypertrophic arthritis are not included in this study, selected cases of calcaneal spurs in gonorrheal arthritis (in which the microscopic changes were indistinguishable from osteochondromas) have been included to emphasize the point that the tissue of origin, and not the etiologic agent is the determining factor in all of these neoplasms.

inflammation. At times the mass will feel much larger than might be expected from its size in the x-ray film. If the bulk of this mass is firm and rubbery, a large proportion of cartilaginous tissue that is invisible in the roentgenogram will be found. If fluctuation is obtained, an overlying bursa containing fluid may be responsible, this bursa being occasionally visualized in the roentgenogram (fig. 4) when there are calcareous deposits in the synovial fluid of the sac.

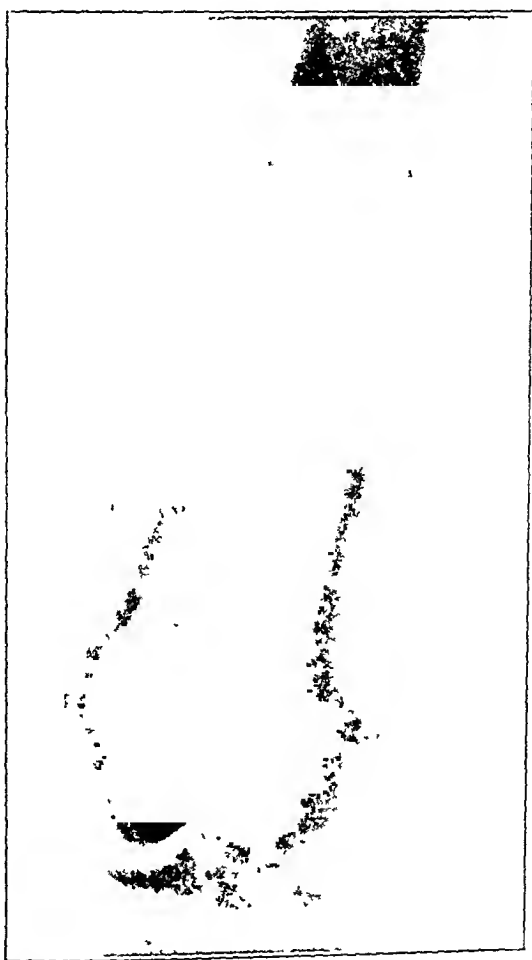


Fig. 5 (P. N. 39602).—Exostosis of the pedicle type at the site of the adductor tubercle in the lower end of the femur. Note the widened metaphyseal region near the outgrowth and the extension of the pedicle in the direction of the pull of the adductor magnus muscle. The osseous portion of the outgrowth is continuous with the underlying normal bone, and the neoplastic cartilaginous cap is well outlined by calcification.

ROENTGENOGRAPHIC FEATURES

The roentgenographic appearance of an exostosis is determined by its mode of attachment to the underlying bone and the size and character of its overlying cartilaginous cap. If the attachment to the underlying bone is by means of a tapering pedicle, the exostosis is usually

referred to as the pedicle type (fig. 5). If the attachment to the bone is represented by a broad area which merges imperceptibly into the shaft of the bone, the exostosis is generally referred to as the broad base type (fig. 6). Occasionally, the exostosis may be attached to the underlying bone by an extremely narrow pedicle, or one which has become fractured and resorbed so that no apparent bony connection is visible in the roentgenogram. This however, is the exception.

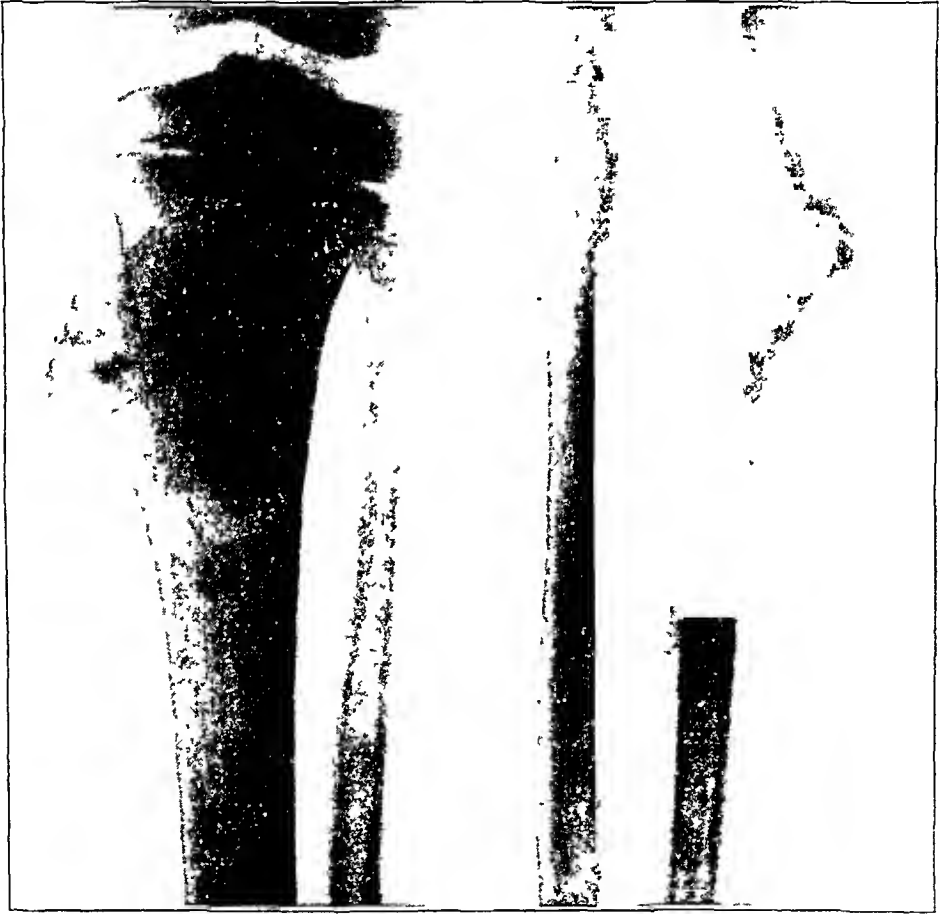


Fig. 6 (P. N. 42142).—The roentgenographic appearance of the broad base type of exostosis. In this case there is a bulging of normal bone over a wide area at what is normally the site of the tibial tuberosity. There is little calcification in the thin overlying cartilaginous cap.

The structure of the pedicle or base of the exostosis is one of its characteristic roentgenographic features. This bony attachment is composed of bone differentiated into cancellous and cortical zones, and these zones are both merged imperceptibly with the normal cortical and medullary portions of the bone beneath. There is much histologic evidence to indicate that the entire pedicle or base of the exostosis is not of true tumor origin but represents an outpouring of normal osseous

tissue through a gap in the overlying periosteum. The most important feature therefore in the roentgenographic appearance of the exostosis when differentiating it from sarcoma is not the bony attachment but the neoplastic cartilaginous cap.

This cartilaginous cap of the exostosis may vary from a small, nearly invisible overlying zone (fig. 6) to a large calcifying cauliflower mass (fig. 7). If this cartilaginous mass is small or if it is definitely or faintly outlined with calcified material, there need be no hesitancy in making the diagnosis of a benign lesion. When, however, the car-

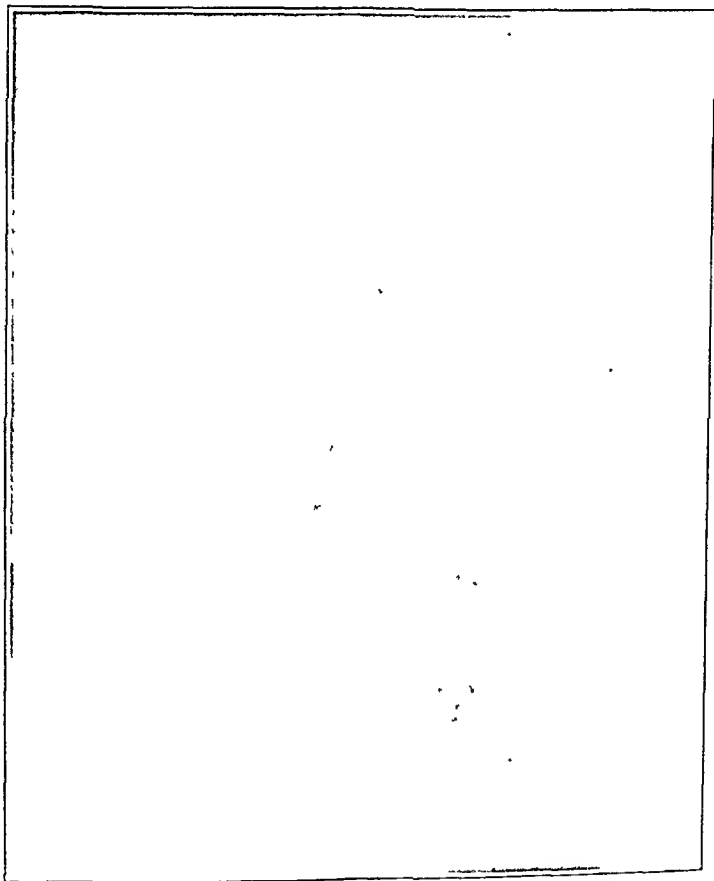


Fig. 7 (P. N. 39064).—Osteochondroma at the lesser trochanter of the upper end of the femur in which the neoplastic cartilaginous cap predominates in the form of a calcifying cauliflower mass. Although this growth bulges into the soft parts in many directions, the absence of bone destruction in the underlying tuberosity and in the base of the exostosis indicates a benign lesion. This picture should be compared to figure 8.

tilaginous mass is large and ill defined on its outward margin and when its calcified areas are being resorbed and present a granular appearance and when, in addition, these more translucent zones are secondarily invading the bony base or pedicle, malignancy is to be suspected, and the symptomatology is to be carefully checked (fig. 8).

In addition to the roentgenographic appearance of the exostosis itself, it is always useful to examine the adjacent metaphyseal region of

the involved bone. A wide metaphyseal zone as pointed out by Jansen⁶ is typical of fully developed or mild degrees of hereditary chondrodysplasia, a diffuse disease of the skeleton with which benign, single or multiple exostoses are often associated.

Exostoses occurring on the shaft side of the long bones, particularly in the region of the thigh or elbow, must be differentiated in the roentgenogram from myositis ossificans traumatica. In ossifying myositis, the ossifying mass has often no attachment to, and is not continuous



Fig. 8 (P. N. 37868).—Osteochondroma at the greater trochanter of the upper end of the femur which has undergone secondary malignant change. Note the granular and hazy outward margin of the calcified cartilaginous cap and the bone destruction mottling the area of the femur just below the trochanters. The patient was a white man, aged 29, who died eight years after the first symptoms with metastases. The roentgenogram was taken three months before death. Compare with figure 7.

with, the underlying bone. It presents a typical parallel laminated appearance and lacks the characteristic cartilaginous cap so often seen

6. Jansen, M.: Dissociation of Bone Growth (Exostoses and Enchondromata) or Ollier's Dyschondroplasia and Associated Phenomena, The Robert Jones Birthday Volume, 43-72, Oxford University Press. London, 1928.

in benign exostosis (fig. 9). The definite history of trauma followed in about six weeks by a hard mass of stationary size typical of myositis ossificans traumatica is an important clinical distinction.

GROSS PATHOLOGY

At operation or after excision, an exostosis has the appearance of a firm lobulated tumor overlaid by a smooth and glistening fibrous surface (fig. 10). If the tumor is cut into, the shiny surface is readily seen



Fig. 9 (P N. 36014).—Roentgenogram in a case of myositis ossificans traumatica. The ossifying mass is separated from the shaft of the underlying bone at the upper and lower portions by a slight interval. There is a definite outward margin to the growth and the densest part of the shadow is streaked in a direction parallel to the underlying shaft. This growth subsequently became malignant and the patient died with metastases.

to be composed of two layers, one a thin fibrous envelop not exceeding 1 mm. in thickness, and the other a translucent cartilaginous zone, generally less than 1 cm. in thickness. Beneath these two layers the bulk of the tumor mass, which is composed of cancellous bone, is found. The relative proportions of cartilage and bone in the usual exostosis is

subject to variation. While it is true that the cartilage composes only a thin cap in most of the tumors, still in other growths this more primitive type of tissue may constitute so much of the bulk that these tumors have been described as periosteal chondromas. The greater the percentage of cartilage in the tumor, the more frequently it is composed of knotty masses or definite lobules (fig. 11).

The relationship of the muscular attachments entering the tumor areas are most significant. The tendon ends are often blended imper-

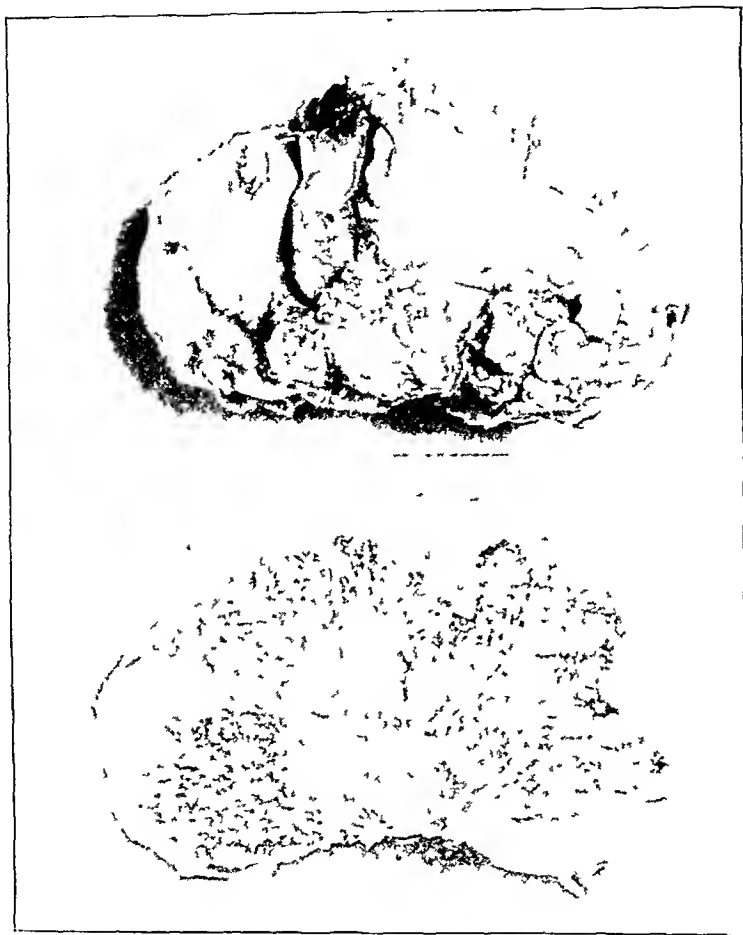


Fig. 10 (P. N. 40040).—Outward appearance and sectioned surface of an excised exostosis. On the outward surface is seen the glistening membrane to which fibers of the tendon have been attached at nodular points. On the cut surface, the thickness of the cartilaginous portion overlying the cancellous bone is plainly visible.

ceptibly with the thin fibrous membrane which overlays the cartilaginous cap. Even under the microscope, this merging of the tendon with the tumor capsule can be seen (fig. 12), and on this relationship hinges largely the conception of the histogenesis of these tumors.

Since under the microscope these growths can be shown to be arising from strands of fibrous tissue, it becomes exceedingly important to

determine the source of this connective tissue and to know whether it springs from tendon, periosteum or aberrant islands of the joint capsule. In the present study, specimens removed at operation were dissected and sections cut from the various margins or zones to determine this relationship of connective tissue to the tumor proper. Two types of fibrous tissue were found in the capsule of the growth. The first was intimately associated with the cartilaginous portions of the tumor, but outwardly infiltrated into the soft parts to become lost in the tendons of the adjacent muscles. The other was also associated with cartilage formation, but its margin extended along the normal bone and merged into the periosteum. In other words, the cartilaginous portion of the tumor seemed to be united by connective tissue to bone on the

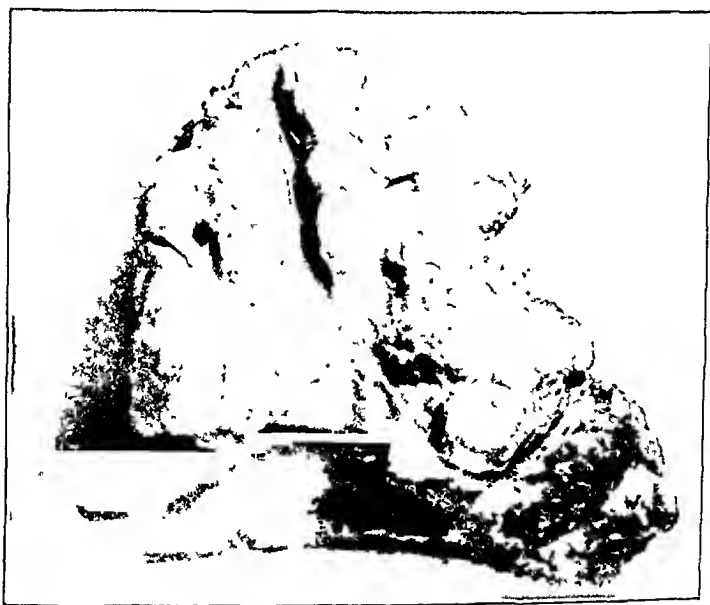


Fig. 11 (P. N. 26392).—Gross specimen showing the nodular and lobulated cartilaginous portions in an exostosis in the upper end of a fibula in a white girl, aged 14. A cure was effected by resection.

one hand and to the tendon ends on the other. From this analysis, it was logical to conclude that these exostoses represented an abnormality in a tissue of union interposed between tendon and bone. Under normal circumstances, this tissue of union is most often a bony protuberance or tubercle provided for the attachment or insertion of an important muscle.

Notwithstanding this interpretation, the way in which the cartilaginous and membranous tissues overlay the bony portion of the osteochondroma in the gross specimen suggests strongly that these tumors represent an abnormal articulating surface of bone. The lobulated contours of the external surface of the tumor are covered by a smooth, glistening layer of cartilage which is analogous to the normal joint



Fig. 12.—Microscopic studies showing the relationship of a benign exostosis to an adjacent tendon. *A* shows a low magnification of an exostosis with a piece of overlying tendon partially encircling the cartilaginous cap. The tendon is seen in the upper left hand corner, and beneath the cartilaginous rim is a large area of cancellous bone enclosing fatty bone-marrow. *B* shows a higher magnification taken from the area marked in *A*. The cellular primitive connective tissue embedded in the tendon is giving rise to cartilage on the one hand and to membranous bone on the other.

cartilage at the end of a long bone, and this outward layer of chondral substance is in turn surmounted by a thin transparent fibrous membrane which duplicates in many respects the perichondrium overlaying the normal articular cartilage (fig. 13). The core of the tumor is com-

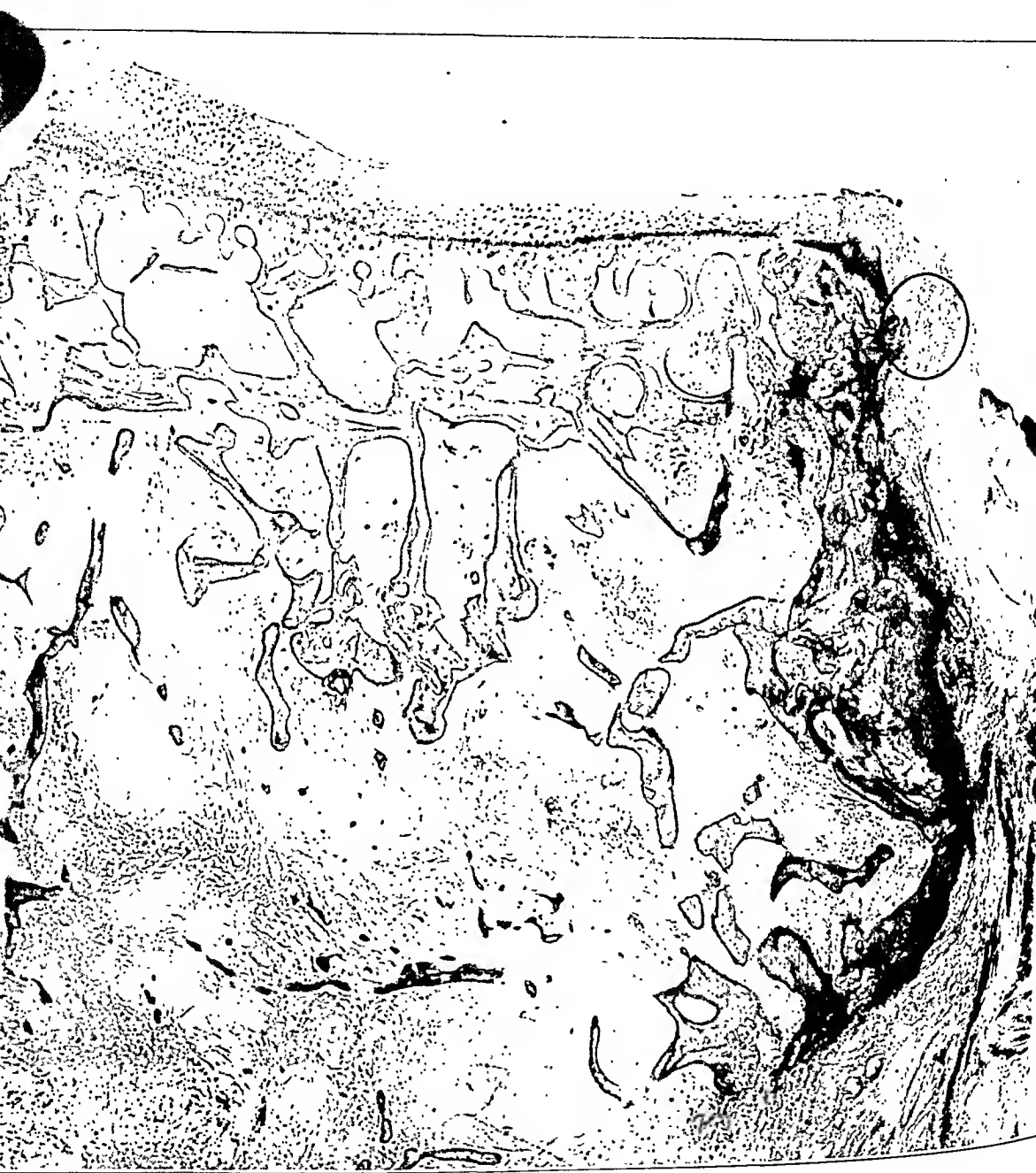


Fig. 13 (P. N. 28770).—Low power photomicrograph of the normal articular surface of the lower radius. The picture shows the joint cartilage, the zone of provisional calcification and the underlying normal bone. Most of the perichondrium overlaying the cartilaginous surface was lost in making the preparation. Note how the transition from cartilage to bone follows the order shown in the exostosis in figure 15.



Fig. 14 (P. N. 28770).—Higher magnification of area marked in figure 13 at the point of reflexion of the joint capsule. At this point there persists primitive precartilaginous tissue giving rise to cartilage. This is a normal growth center.

posed of cortical and cancellous bone which for all practical purposes is identical with normal osseous material at the articular ends of bone. To emphasize further this analogy, at operation an overlying bursa is not rarely encountered over the exostosis, which simulates the bursae associated with normal joints.

This composite interpretation of the gross specimens of osteochondromas, relating them on the one hand to exaggerated normal bony

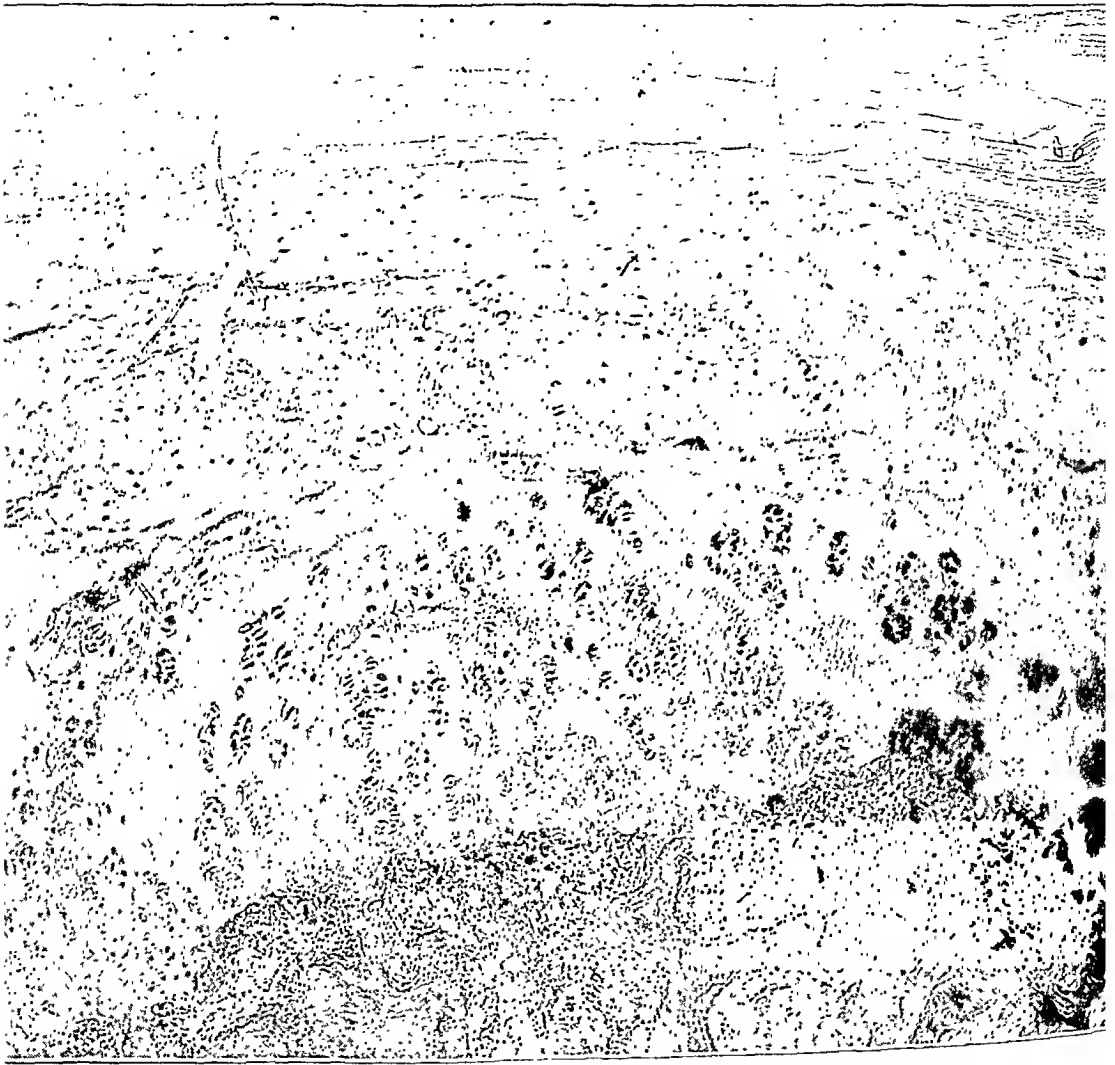


Fig. 15 (P. N. 26392).—Photomicrograph from the specimen shown in figure 11. The overlying membranous portion of the exostosis shows in the upper right hand corner the direct continuation of fibers of an adjoining tendon. The entire histogenesis of the neoplasm can be traced in this picture. At the upper margin is the primitive connective tissue which is the mother substance of the tumor. This tissue is giving rise to a small amount of fetal cartilage, beneath which there is much typical normal adult cartilage, calcifying in its deeper layers. Beneath this, there is a protusion of normal adult bone enclosing a small amount of fatty marrow.

protuberances, and on the other to supernumerary articular surfaces, is justifiable on the basis of their histology as well as their gross pathology. For histologically, these tumors are derivatives of a primitive periarticular tissue which normally serves such multiple functions.

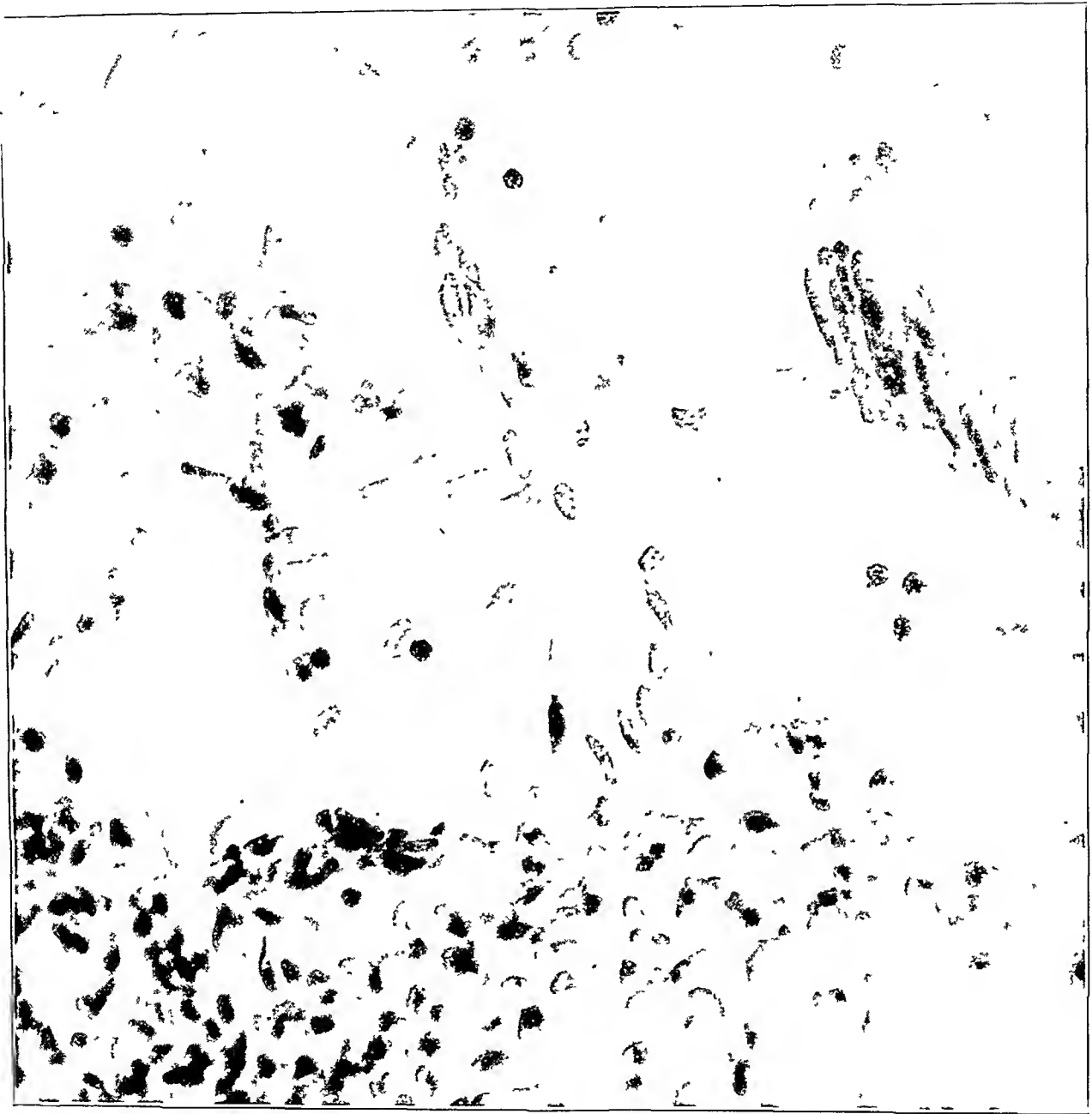


Fig. 16 (P. N. 41267).—High power photomicrograph of a cellular area at the membranous margin of an exostosis. The dense cluster of spindle cells near the upper right hand corner are embryonic connective tissue cells. The clear space beneath is the hyaline substance of myxoma and the three cells with the dense nuclei are fetal cartilage cells. This illustrates the transition from connective tissue to cartilage (the myxoma phase) which is the neoplastic process in osteochondroma and in all tumors of the fibrocartilaginous group.

MICROSCOPIC FEATURES

The typical microscopic picture of the osteochondroma seen under low magnification is shown in figure 15. The tumor, passing from the superficial layers to the deeper ones adjacent to the normal underlying bone, shows a characteristic transition from fibrous tissue to cartilage to bone. The most superficial layer is generally a hyalinized connective tissue, very poor in nuclear material, which caps the tumor over its outward surface. At points in this cap, there are islands of more cellular connective tissue which, when put under high power magnification, show many small spindle-shaped nuclei arranged in syncytial fashion, resembling myxoma (fig. 16). Beneath the fibrous layer is found a hyalinized cartilaginous substance. In the regions where the connective tissue is cellular, there are numerous fetal cartilage cells, but these small areas of fetal cartilage are insignificant beside the major portion of chondral tissue which is of the adult variety and resembles in all respects the typical chondroma. In its deeper portions this cartilage undergoes calcification, and abutting on the zone of calcified cartilage laminated bony spicules are to be found. This laminated adult bone is cancellous in structure with a generous amount of fatty bone-marrow between its trabeculae. Osteoblasts are generally not applied to the spicules, nor has this bone the coarse fibrous structure typical of new bone formation.

The entire microscopic picture is preponderantly one of quiescence, the varying histologic zones appearing like the stratified deposits of an obliterated sea. It is only in isolated zones that evidence of active proliferation persists. This is in keeping with the clinical characteristics of these tumors which are slow in their growth and mild in the symptoms provoked. These isolated areas of cell proliferation, however, are the points most important for the study of the histogenesis of these neoplasms and must be considered in more detail. They also supply a nucleus for the malignant change that occasionally occurs in these tumors.

In the areas of cellular fibrous tissue, the capsule dips into the tumor, dividing it into lobules. These penetrating strands of connective tissue give rise to groups of fetal cartilage cells and also in rare instances to small amounts of new bone. It is therefore plainly evident that the mother substance of the cartilaginous portion of these tumors is the precartilaginous connective tissue found indenting the tumor from its periphery. Although this early connective tissue must also be ascribed the function of new bone formation, it is by no means certain that the large amount of adult bone comprising the bulk of the exostosis is derived from this same mother substance. The entire mass of this adult bone is so intimately related with the shaft of the underlying normal bone that it appears to be arising as a protrusion of the shaft, rather than as a deposit of the small amounts of osteogenic tissue

found in the neoplastic portions of the cartilaginous cap. If this interpretation is correct in the histogenesis of these tumors, it becomes necessary to explain not only the origin of the cartilaginous growths that form the cap of the exostosis, but also to account for the independent proliferation of normal bone beneath which constitutes the pedicle or base of the osteochondroma.

HISTOGENESIS

The close simulation of the usual exostosis to a normal articulating surface of bone, as well as the relationship that the location of the tumor

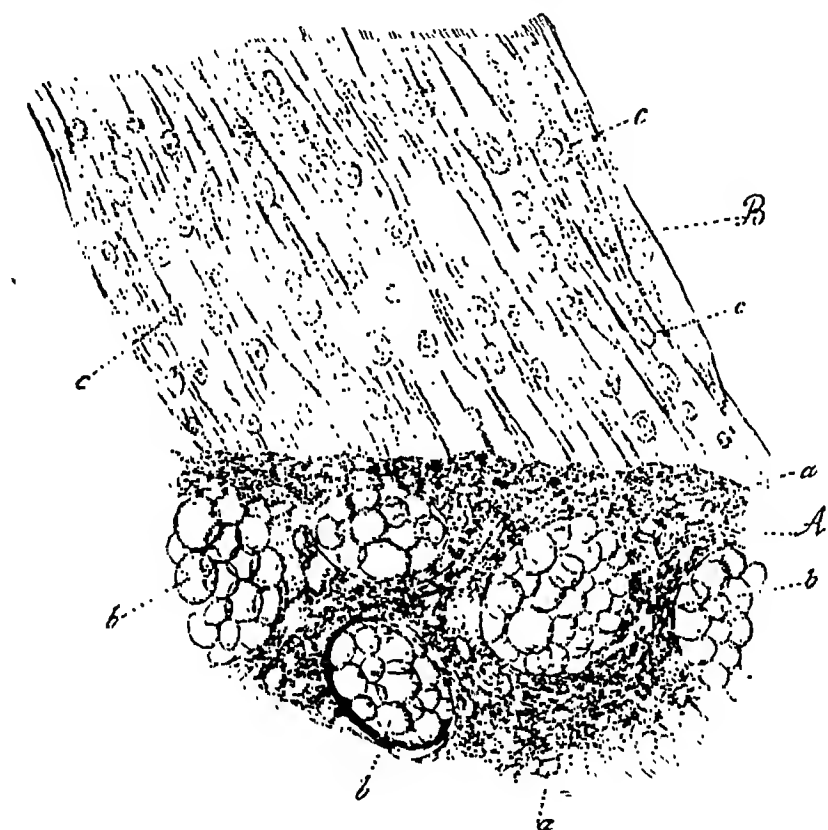


Fig. 17.—This drawing reproduced from Kollicker depicts cartilage cells (*c*) in the end of the achilles' tendon (*B*) which attaches directly to the bone of the os calcis (*A*). This is the first known record of the discovery of precartilaginous connective tissue giving rise to cartilage in the substance of a tendon. (After Kollicker: *Human Histology*, London, Sydenham Society, 1853, vol. 1, p. 251.

generally has to points of tendinous attachments, focus attention on the embryology of these normal structures. In both normal tendons, which attach directly to bone, and in normal joints at the reflexion of the joint capsule, proliferating zones apparently acting as normal growth centers may be found. In these proliferating centers early cartilage cells derived from young fibroblasts may be seen (figs. 13 and 14), and occasional areas of ossification, a transition of tissues typical of

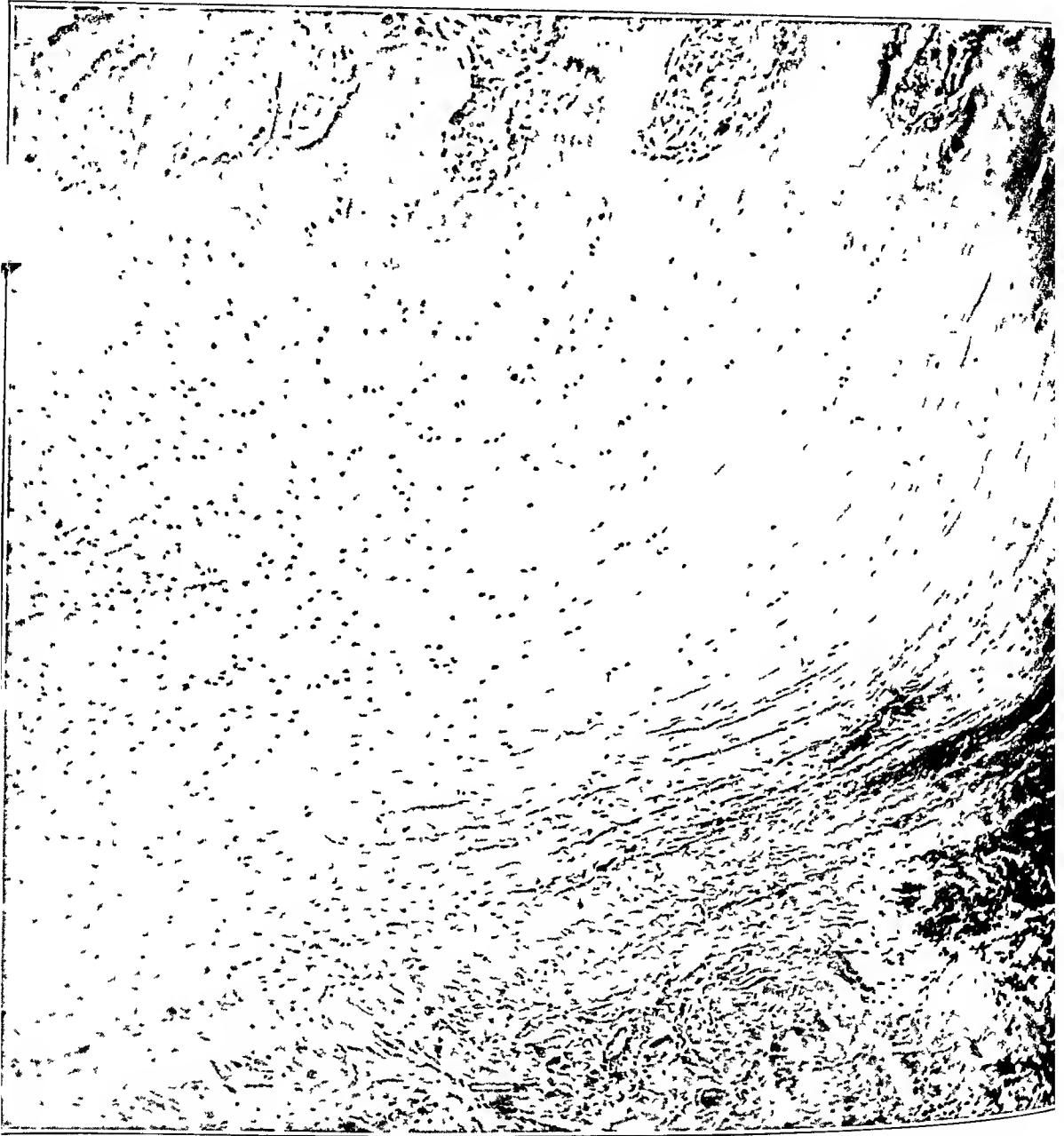


Fig. 17A (P. N. 48035).—Low power photomicrograph showing the attachment of the extensor carpi radialis longus to the metacarpal in a white man, aged 31 (the hand was amputated for a sarcoma of the soft parts occurring in another portion of the hand). The illustration shows the persistence of primitive cartilaginous connective tissue with the proliferation of cartilage, forming a junction between the bone in the upper portion of the picture and the tendon in the lower. This embryonic tissue of union between tendon and bone, which can be observed microscopically under normal conditions at the site where chondromyxosarcomas arise, refutes the current misconception in regard to the origin of such tumors by a process of dedifferentiation.

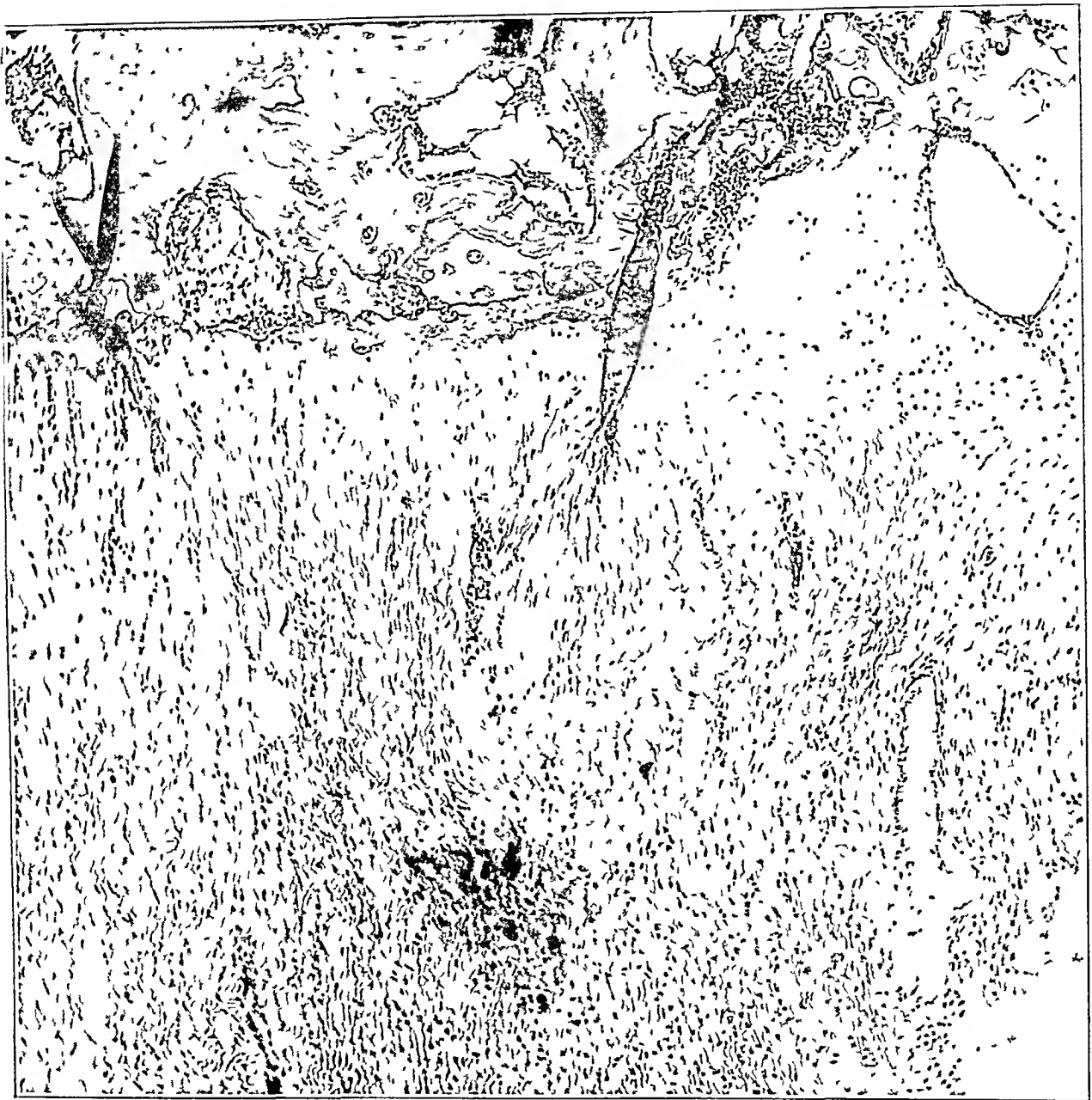


Fig. 17B.—Low power photomicrograph showing precartilaginous connective tissue with cartilage formation at the insertion of the quadriceps tendon into the tibial tuberosity in a young dog. This photograph should be compared with figure 17A. The embryonic tissue of union shown in this picture persists in practically an identical form even in later life as shown in figure 17A.



Fig. 18.—Osteogenic processes in tenosynovitis associated with calcareous bursitis. In the lower right hand corner is seen dense embryonic fibrous tissue which is proliferating cartilage that is undergoing calcification and ossification. (After Harbin: *Arch. Surg.* **18**:1510 [April] 1929).

the osteochondromas. The occurrence of such proliferating zones in normal tendon ends was first observed by Kollicker⁷ in 1853 (fig. 17) and similar transitional zones are typical of tenosynovitis associated with calcareous bursitis (Harbin,⁸ fig. 18). In the development of joint mice, the studies of Henderson and Jones⁹ demonstrated that loose cartilaginous bodies may undergo ossification in the synovial membrane (fig. 19), showing again the relationship of the histologic transitions typical of exostosis to articular and periarticular structures.

Since in normal bones the growth centers at the epiphyseal line contain neither proliferating fibrous tissue nor fetal cartilage cells but

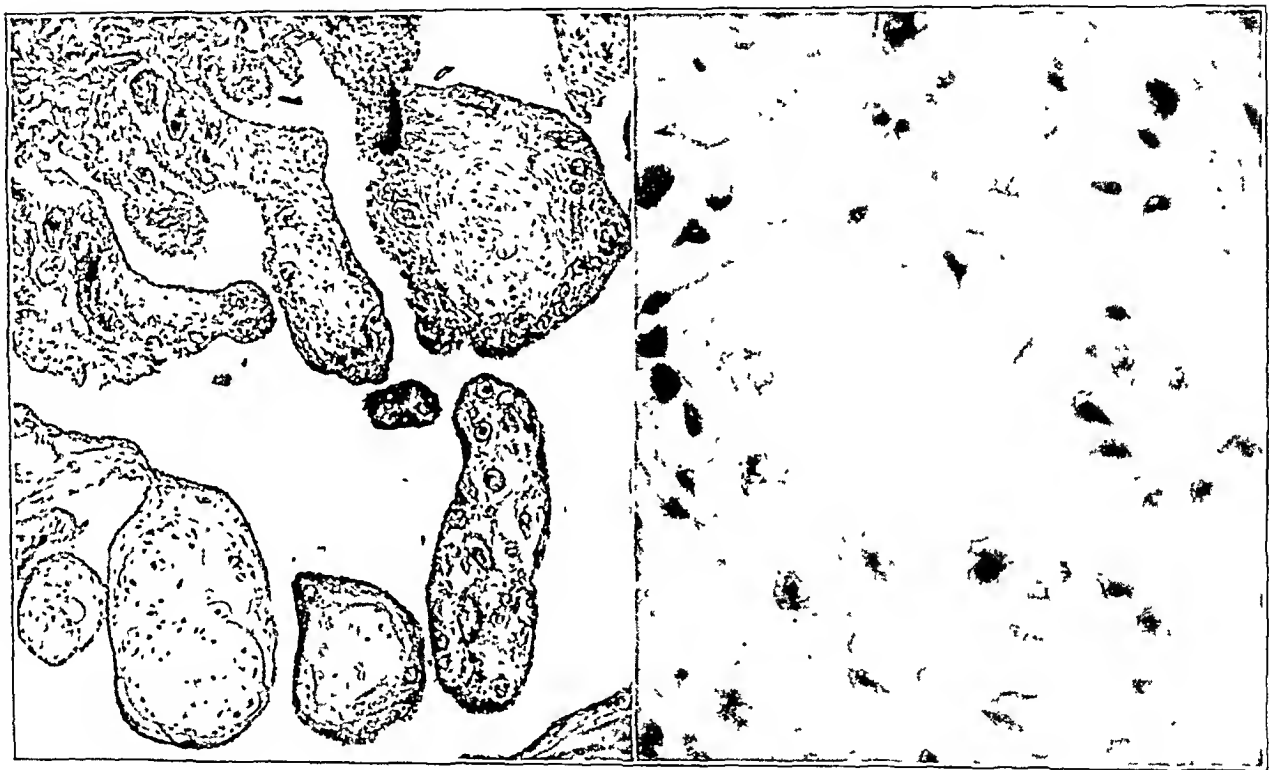


Fig. 19.—Low and high power photomicrographs showing the development of cartilage with subsequent ossification in tags of synovial tissue within the joint cavity. This illustrates the histogenesis of the so-called joint mice occurring in osteochondromatosis of the knee joint and proves the power of cartilage formation residing in the primitive connective tissue of the synovial membranes. (After H. T. Jones: *J. Bone & Joint Surg.* 6:407, 1924.)

7. Kollicker, A.: *Manual of Human Histology*, London, Sydenham Society, 1853-1854, vol. 1, p. 251.

8. Harbin, R. M.: Deposition of Calcium Salts in the Tendon of the Supraspinatus Muscle, *Arch. Surg.* 18:1491 (April) 1929.

9. Jones, H. T.: Loose Body Formation in Synovial Osteochondromatosis, with Special Reference to Etiology and Pathology, *J. Bone & Joint Surg.* 6:407, 458 (April) 1924.

derivatives in a higher state of differentiation, it is evident that the osteochondromas are not related histogenetically to the bone proper nor to the epiphyseal line as so often stated, but rather to such articular and periarticular structures already cited. This deduction is confirmed by a comparative study of the embryology of the joints, periarticular structures and bone.

Both the bones and joints begin their differentiation from a single type of mesenchymal derivative. This mesenchymal derivative is a simple condensation of embryonic connective tissue which forms at the site of the future skeleton (fig. 20). It represents the precartilagin-

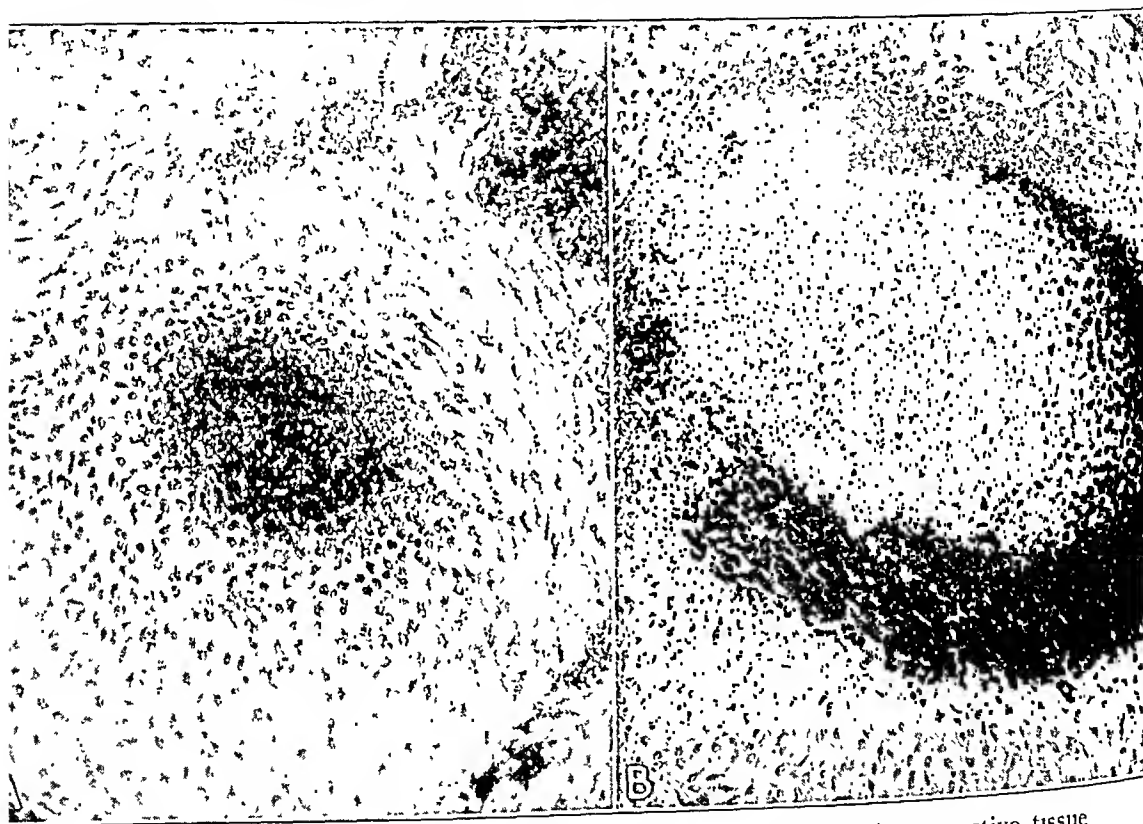


Fig. 20.—Embryo. *A* shows the condensation of embryonic connective tissue (blastema) at the site of the future skeleton, and in *B* this precartilaginous condensation of connective tissue is giving rise at its center to early cartilage cells. The persisting rim of dense connective tissue about the early cartilage cells is the primitive perichondrium and has the power of forming both bone and cartilage. Persisting strands identical in nature with the perichondrium are referred to as precartilaginous connective tissue throughout this paper. The sections were taken from a human embryo 14 cm. in length.

ous state of the future skeleton and is known as blastema. Whereas the blastema of the future skeleton differentiates rapidly into cartilage so as to form an entire cartilaginous skeleton (with exception of the membranous bones) at an early date in embryonic life, the so-called extraskeletal blastema, which is destined to form joints, and the attachments of certain tendons and ligaments lags behind and goes through a

somewhat different cycle of changes. By mucoid regression in this extraskeletal blastema, the joint cavities and certain bursae are formed, and this same embryonic fibrous tissue overlays the joint ends of the bone with the perichondrium from which the joint cartilage is formed on the underlying bone. Where this thick connective tissue coat overlaps and extends beyond the bone, the joint capsule, the ends of ligaments and tendons and the synovia are differentiated.

Thus the joint cartilage, the joint capsule, the synovia, the ends of various ligaments and tendons and the joint cavity as well as associated bursae are all derived from this one mother substance. This extraskeletal blastema tissue in all of its derivatives retains at points the power of cartilage and bone formation throughout life. But unlike the skeletal cartilage differentiated from this blastema at an earlier stage, this type of chondral tissue does not undergo active resorption by giant cells in its calcified state, but becomes converted more directly into permanent bone.

Thus on embryologic grounds, as well as by site and location, the osteochondromas, because of the histologic cycle from fibrous tissue to cartilage to bone which they show in their growth zones or cartilaginous caps, must be histogenetically related to the extraskeletal blastema or the forerunner of articular and periarticular structures.

In tendons such as the achilles, the quadriceps at its attachment below the knee and the adductor magnus fastening above the medial condyle of the femur union is established not with the periosteum, but directly to bone. These tendons have their osseous ends formed not by ordinary fibrous tissues, but by extraskeletal blastema (Fig. 2), and since the periosteum is normally lacking or deficient at such points, the underlying bone lacks a limiting membrane and grows out in the form of a normal bony protuberance to meet the tendon. These outgrowths of bone are normal occurrences and are known as the tibial tubercle, the tibial tuberosity, etc. The entire tuberosity, which provides for such ligamentous attachment, however, is not derived from the underlying bone but is added to more indirectly from processes formed from the blastema in the ligament or tendon. Both the end of the bone and the end of the tendon thus cooperate in the formation of the tuberosity.

Therefore, the normal events at the site of a fracture, which must be superseded in order for tumor formation, are: (1) the end of a tendon or ligament formed from blastema

10. Macewen (The Growth of Bone: Observations on the Power of the Periosteum to Act Thus as a Limiting Membrane, Experimental Inquiry into the Development and Reproduction of Bone, Glasgow, James Maclellan & Son, 1912) has experimentally demonstrated the power of the periosteum to act thus as a limiting membrane.

tissue and destined to aid in the formation of its own bony attachment; (2) an underlying zone of normal bone without periosteal covering destined to form an outgrowth or attachment point in the skeleton; (3) a margin of periosteum surrounding the zone which eventually is to form a sleeve or cuff about this zone.

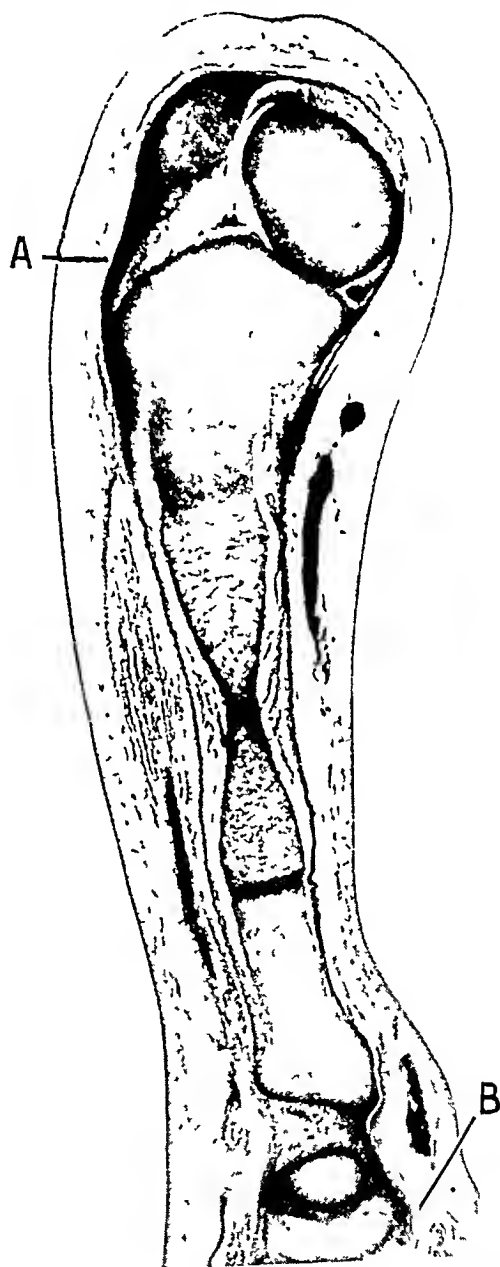


Fig. 21—Low magnification of a longitudinal section of the lower leg of the embryo shown in figure 20. The future skeleton is preformed in cartilage. The entire tibia is shown, the cartilage of which is undergoing calcification in the pinched, midshaft region. At *A* is seen the insertion of the quadriceps tendon (embedding the patella) into the future tuberosity of the tibia. The dense black connective tissue of the tendon is persisting precartilaginous connective tissue shown under higher magnification in figure 20. At *B* is seen the dense primitive connective tissue in the region of the insertion of the achilles' tendon. Note the persistence of this dense connective tissue within the future knee joint.

The origin of an osteochondroma or exostosis at such transitional zones depends on abnormal variations in some one of the foregoing factors. If both the zone of cartilage in the tendon end and the bony outgrowth of the underlying bone are normally balanced and eventually overlaid by periosteum, an osteochondroma will not form. If, however, the periosteum surmounts only the outgrowth of the underlying bone and fails to blend with the fibrous tissue of the tendon, the growth of the cartilaginous center in the fibrous attachment of the muscle will not be properly limited, and a tumor results. In such an event, the cartilaginous zone in the tendon overgrows the protuberance of normal bone, overlapping the periosteum and forming a typical exostosis.

It is clear from the foregoing facts that osteochondromas are compound growths, since the underlying osseous pedicle is composed of normal bone which has a deficiency in its periosteal covering, while the overlying cartilaginous cap arises independently from precartilaginous connective tissue in the end of a tendon or ligament.

ETIOLOGY

From a consideration of the histogenesis involved in tumors of the osteochondroma group, the multiplicity of possible etiologic factors becomes apparent. In congenital exostosis, in which these tumors are frequently multiple and often hereditary, there is undoubtedly a tendency to variation in the periosteal apertures about the zones where bony protuberances normally arise. That this congenital variation affects the periosteum and underlying cortical bone primarily as well as the cartilaginous zone of growth in the ligaments and tendons is evidenced by the diffuse metaphyseal widening so often seen in this form of so-called hereditary, deforming chondrodysplasia. Apparently the rim about the periosteal deficiency is either unusually wide or abnormally inactive or both, permitting the underlying bone to protrude in an unusual manner.

In regard to the exostosis of inflammatory origin, such as the calcaneal spurs in gonorrheal arthritis, the fault in this instance is not a deficiency in the activity of the adjacent periosteal cuff but rather an overstimulation of the cartilaginous center in the tendon where the infection has directly initiated an increased growth activity. Likewise, in the osteophytes of chronic arthritis, there is a stimulation of the normal zones of cartilaginous growth which persist near the point of reflexion of the joint capsule and synovial membrane. Despite the unorthodox procedure of classifying these infectious osteophytes with the neoplasms of the osteochondroma group, microscopic distinction between the

two is impossible, and histogenetically, as has just been shown, there is a common basis of origin (fig. 22).

Single exostoses may arise as a result of traumatism to a normal cartilaginous growth zone or where aberrant islands of cartilage with strands of blastemal tissue have been left behind to form embryonic cell rests in the sense of Cohnheim. When traumatism plays an etiologic

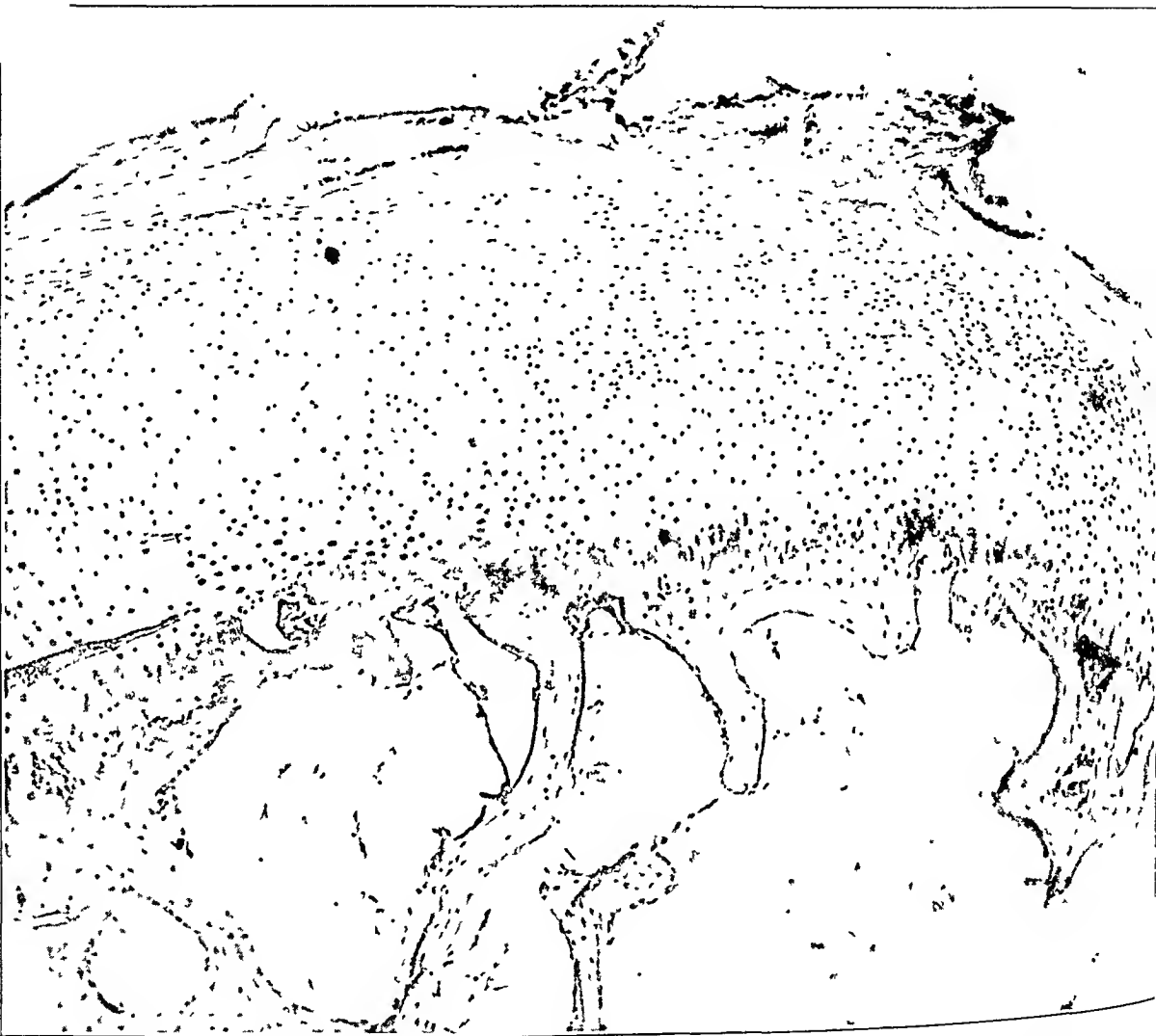


Fig. 22 (P. N. 34167).—Low power photomicrograph of a calcaneal spur in a white man, aged 39, giving a history of gonorrhea thirteen years previously followed by polyarthritis for a number of years, which at first affected all the joints but which finally localized at both ankles. In the picture there is seen the overlying connective tissue continuous with the tendon, the zone of cartilage and the underlying bone typical of all exostoses. Compare this with figure 15.

rôle, it is difficult to determine whether the traumatism is active in repressing the adjacent periosteum or in stimulating the adjacent zone of cartilaginous growth. Conceivably, the injury may result in both, but the latter is more probable. At any event, the trauma probably

functions in disturbing the balance between the permanent bone formation in the underlying osteogenic zones of the periosteum and the proliferating powers in the adjacent precartilaginous tissue.

TREATMENT AND PROGNOSIS

The foregoing analysis of the histogenesis and etiology of exostoses has an important bearing on the treatment and prognosis of the disease. Ordinarily these lesions are benign and represent merely an imbalance between two normal phases of growth in the same manner, as was pointed out in a previous paper in regard to bone cysts and giant cell tumor (Geschickter and Copeland¹¹). Operative intervention is frequently not called for, since in the usual exostosis the periosteum and underlying cortical bone succeed eventually in "hemming in" the cartilaginous cap except at the point where the fibrous portions of the tendon or ligament perform an identical function. However, even when such normal balance is restored, operative removal may become necessary because of the interference by the tumor with the function of the surrounding muscles in the use of the adjacent joint. When the location of the tumor is such that repeated injuries result in the formation of a bursitis, the consequent painful lesion warrants operative removal.

In the removal of such an exostosis, a more careful dissection is warranted than is usually given such tumors. The zone of periosteum overlying the adjacent normal bone about the pedicle or base should be carefully delimited and marked out by the knife and laid back. The base or pedicle should then be chiseled through and the tumor lifted off the underlying bone while it is still attached to strands of the adjacent tendon. The fibers of the tendon entering the tumor zone should then be partially dissected and clipped above the cartilaginous zones which are frequently embedded in them. After the growth has thus been removed, care should be taken to provide for the reanchoring of the strands of the tendon and to suture the adjacent fascia and muscles over the rift in the periosteum to aid in the restoration of the normal cortex when healing occurs.

Ordinarily, the usual exostosis, when operated on, is accorded no such systematic treatment. The tumor is chiseled away piecemeal in a careless fashion, the surgeon neglecting the relationship of the adjacent tendons to the tumor. The result is that recurrences of such benign exostoses are by no means rare (5 per cent of this series), and when recurrence does not take place, the adjacent cortex often reforms in an irregular and troublesome manner (fig. 23).

11. Geschickter, C. F., and Copeland, M. M., with foreword by Bloodgood, J. C.: Osteitis Fibrosa and Giant Cell Tumor, *Arch. Surg.* **19**:169 (Aug.) 1929.

While many exostoses do not require operation and cures are commonly effected in those with aggravated symptoms by simple surgical removal, there is a third group in which both the prognosis and the treatment are an entirely different problem. This is the group of benign osteochondromas which undergo secondary malignant change. In the present series of cases, malignancy arose in over 7 per cent of these benign exostoses or osteochondromas. This is a far higher percentage than is generally conceded, but the reason for this increase in the per-

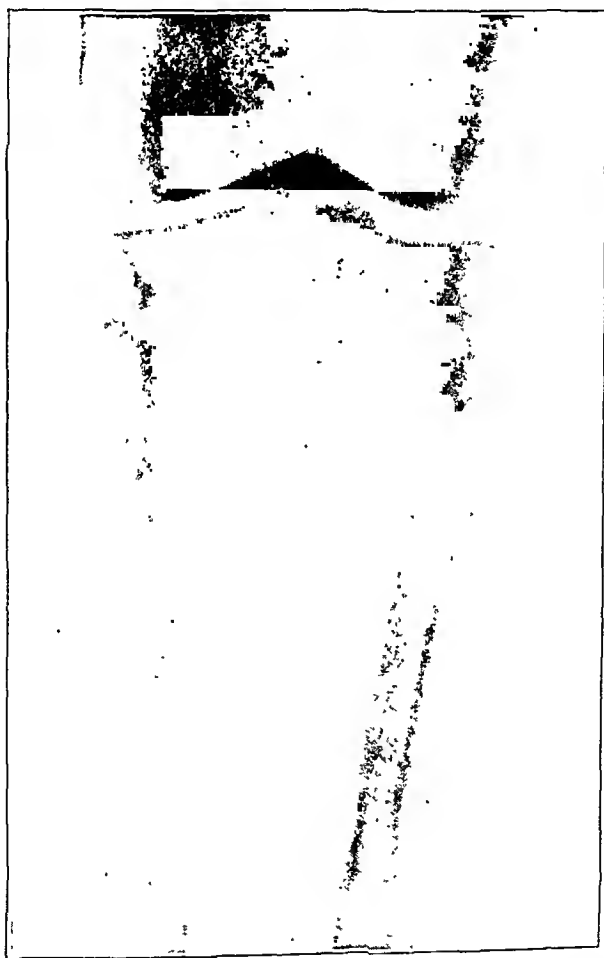


Fig. 23 (P. N. 35720).—Roentgenogram taken ten months after complete excision of the exostosis shown in figure 4. Note the gradual reformation of bone escaping through the periosteal gap at the site of the former exostosis.

centage of malignancy in the present series is due to the method in which they were studied.

It is not sufficient to follow up the cases of benign exostoses and to find out in which of them the patients subsequently die of sarcoma developing in the original lesion. The usual benign exostosis which comes under the observation of the physician or surgeon is removed, and this removal usually eventuates in healing so that the possibility of malignancy is obviated. In patients discharged without treatment or

who have recurrence after removal there is, of course, the possibility of malignancy. But there is also a still larger group of cases that never come under the observation of any physician until malignant change has occurred. To determine this third group, it is necessary to examine carefully the roentgenograms and specimens in all cases in the osteogenic sarcoma group and to isolate those cases which show evidence of arising in a previous osteochondroma. It is this third group of cases (table 6) in which most of the osteochondromas terminating in sarcoma were found.

In view of this fairly large percentage of cases with malignant change, the question arises whether or not the removal of an exostosis is warranted as a preventive measure. Such a wholesale removal of these growths is not favored on the basis of the present study, but attention is called to the need of following cases in which operation has not been performed and of informing the patient to return at once if he observes any unusual increase in the growth or an aggravation of symptoms. In addition, tumors which are discovered in the roentgenogram in and about the pelvis or about the spine should be removed or followed by repeated roentgen examinations twice yearly because their location makes any increase in size dangerous to the patient.

While the age of the patient is a factor in the sarcomatous transformation of these neoplasms, it does not serve as a guide in the rendering of a prognosis. In persons between 15 and 20, the growth impetus following adolescence may stimulate these tumors directly, and in patients over 40 the loss of the proliferating powers in the periosteal regions of the exostosis makes stimulation by trauma or infection of the tumor more dangerous. This permits the malignant change to occur at almost any age.

MULTIPLE EXOSTOSES OR HEREDITARY DEFORMING CHONDRODYSPLASIA

In the foregoing discussion of osteochondromas or single exostoses, an analysis was made which emphasized not the cartilaginous or the osseous portions of these tumors, but instead, their derivation from a precartilaginous connective tissue concerned with periarticular functions. Although this precartilaginous connective tissue is visible only in remnants at the periphery of these tumors, it is nevertheless the mother substance of the cartilaginous mass that has received so much attention by other authors. This tendency to emphasize the chondral substance of these tumors instead of their connective tissue origin, particularly when they assume the form of the so-called multiple cartilaginous exostoses or hereditary deforming chondrodysplasia, has been the cause of much confusion in the attempts to interpret the nature of this multiple skeletal disease.

Hereditary deforming chondrodysplasia (a term given by Ehrenfried³) denotes a distinct clinical form of exostosis in which the multiple occurrence of such tumors in a single patient is accompanied by numerous other skeletal deformities, such as bending and shortening of the bones and widening and irregularity of their metaphyseal ends. This form of the disease known in the literature under many different terms is congenital, and is usually discovered in childhood. The hereditary factor is extremely prominent and has been traced through as many as four or five generations. The mode of transmission is direct but somewhat variable, and apparently both males and females may transmit the disease. The fundamental basis of the congenital disturbance is obscure, but deficiencies in the periosteum and a tendency for the perichondrium to persist and to function as such, together with precartilaginous connective tissue about the joints, seem to be responsible for most of the deformities.

CLINICAL FEATURES

Although the disease is active throughout the developmental period of skeletal growth, the actual age of observation varies according to the time when the physician is first consulted. Usually the patient comes under observation between the ages of 9 and 20, but the disease has been reported as early as the age of 4 years and as late as 80. The deformities affect primarily only the bones derived from cartilage and involve most markedly the bones of the forearm and foreleg, although the femur and humerus rarely escape. Most of the exostoses are found in the cortical region of the bone, resulting in a widening of the shaft at these points and giving rise at their base to areas of either increased or decreased density. In addition to the outward projections at these points, there may be an inward growth resulting in the formation of central chondromas. The last named have often been mistaken for cysts of the bone. Where two adjacent bones are affected, as the radius and ulna or the tibia and fibula, fusion may occur between the expanded and distorted areas of the cortex (fig. 24), the lesser bone (fibula or ulna) usually suffering arrested development.

In well developed cases, the outstanding symptomatology relates to the deformity or so-called "family mark," which consists in shortening of stature and crookedness of the arms or legs. As the disease progresses, one or more of the osteochondromas, because of continued growth, will impinge on important structures, causing pain and dysfunction. One of the common disturbances of such impingement is a resulting paraplegia or local paralysis. Exostoses about the spine may result in either a spastic or a flaccid paraplegia, while local growths in the region of the knee by pressure on the peroneal nerve may give rise to paralytic clubfoot. In rare instances, an aneurysm has developed as a result of a constant trauma to an adjacent vessel.

Variability characterizes the more marked symptoms of the disease. During the youth of the patient, painful growths may continue to arise, to decrease finally or nearly disappear after the patient reaches maturity. While the deformities tend to become stationary in adulthood, exacerbation of symptoms may be produced by local irritation to an under-

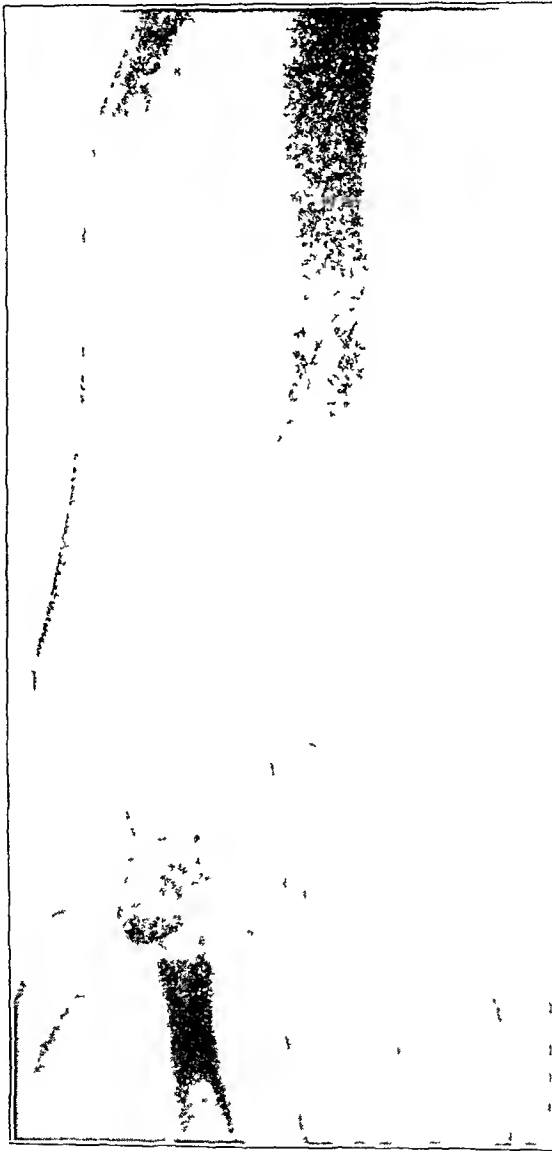


Fig. 24 (P. N. 28246).—Case of congenital multiple exostosis showing fusion between the lower end of the radius and the lower end of the ulna. Note the bending and distortion of the bones of the forearm and the undeveloped state of the distal end of the ulna.

lying growth. As pointed out for single exostoses, an increase in the severity of symptoms after the age of 30 in a previously dormant osteochondroma may be the first sign of a malignant change.

Unless neurologic manifestations are present, examination of the patient usually shows few systemic features of clinical interest other than those relating to the skeleton. Unlike chondrodystrophia fetalis, there is no alteration of the physiognomy and no deformity of the head, although congenital anomalies, such as a deficiency of the bladder sphincter, may be present. The bones of the trunk are usually not markedly involved by the disease, although exostoses affecting the spine and ribs are occasionally recorded. In the extremities there is a tendency for a fairly symmetrical bilateral involvement, although unequalness in the length of either arms or legs is not rare. Full extension is often limited, and there is bowing of the forearms and often of the forelegs. Deformities of the hands and feet, particularly in the phalanges, are common. Definite hard and knotty outgrowths attached to the bone may be palpated, usually near the ends of the bones but occasionally near the region of the midshaft. The quiescent growths are less than the size of a fist, but progressive osteochondromas in which malignancy may be suspected may exceed the size of a child's head.

ROENTGENOGRAPHIC FEATURES

In the x-ray films taken of this condition, numerous typical osteochondromas, involving the metaphyseal region of the long bones of the extremities, are found. These outgrowths may appear in clusters about a given region and beneath the point of these exostoses, the shaft of the bone is widened and the cortex frequently thinner than normal. The exostoses vary in configuration, some being of the pedicle type, others a cauliflower-like growth with a broad base, and still others rounded, elevated areas near the deformed end of the bone (fig. 25).

In the ulna or fibula, bending is usually marked, and there is an arrest of growth showing shortening and failure of the epiphyseal ends to develop properly (fig. 24). In the ulna, it is usually the lower end of the bone which is deficient, and it is in this region that fusion with the radius often takes place. In the fibula, the upper end is most frequently affected, and synostosis with the tibia may result. Although the entire end of a bone, such as the lower end of the ulna, may be distorted by these outgrowths and the thinning of the cortex, and the foamy area in the base of the exostosis may resemble a cyst, true cysts of the bone such as those seen in osteitis fibrosa have not been recorded in the present series, and to my knowledge there is no verified record in the literature of such a cyst despite several erroneous references recently published.

This is one of the easiest conditions in the entire bone tumor group to diagnose in the roentgenogram. The three salient features determining the diagnosis are: the formation of typical exostoses of the pedicle or broad base type, the widening of the metaphyseal ends of the long bones and the deformity with bending and fusion of the ulna or fibula.

in the forearm or foreleg. The appearance of the bones about the knee is typical (figure 25). The lower end of the femur is squared off, and the exostoses projecting therefrom are directed upward in the direction of the muscle pull. The upper end of the tibia is similarly distorted, the outgrowths in this instance pointing downward. The

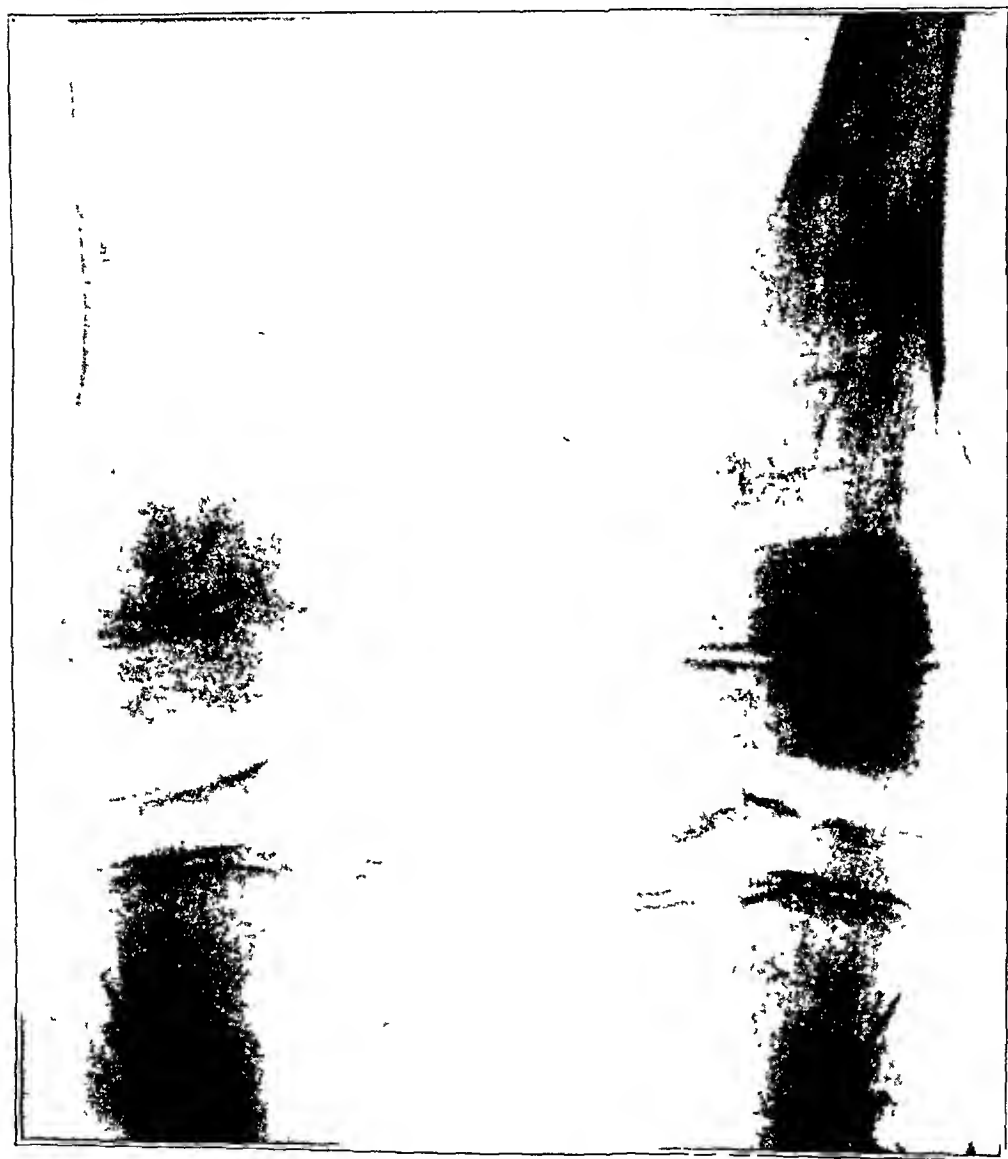


Fig. 25 (P. N. 28539).—The bones about the knee joint in a case of hereditary, deforming chondrodysplasia. In addition to the numerous exostoses, note the widening of the metaphyseal ends of the bone which gives to the lower end of the femur and upper end of the tibia a characteristic squared-off appearance.

upper end of the fibula is expanded and often fused with the end of the tibia.

The possibility of malignancy in these conditions is a much disputed point. If malignancy occurs, it is never generalized or multiple in

focus, but arises in a single osteochondroma, and for this reason differs in no way from the possible malignant change discussed under single exostoses.

Apart from the cases of typical hereditary deforming chondrodysplasia with its outspoken manifestations, there are occasional non-hereditary cases in which several cartilaginous tumors may affect a single bone or several widely separated bones. Rarely such instances are observed in which multiple chondromas of the hand are associated with exostoses in the arm or another long bone. More frequently, several exostoses in a single region of one bone have been observed. Associated with such a nest of lesions, there is the same metaphyseal widening seen, as in hereditary deforming chondrodysplasia, and there may also be bending and deformity of the bone. Such cases are best referred to as multiple exostosis or simple chondrodysplasia, and represent a transitional group of lesions midway between single osteochondromas on the one hand and multiple exostosis of the hereditary deforming chondrodysplasia type on the other.

PATHOLOGY

Adequate study of the gross pathology of these lesions is difficult owing to the scarcity of material. Since the disease is ordinarily not fatal and operation, when performed, is restricted to a single lesion, a detailed study of many bones has rarely been made. In general, the pathologic process of the local growths is the same as that described for the single osteochondroma. The important points of difference are the multiplicity of the tumors, the frequency with which cartilaginous masses are found embedded in the medullary and subcortical regions of the bone beneath the exostoses and the bending and distortion of the long bones, particularly the ulna and fibula (fig. 26).

The widening of the metaphyseal region and the distortion of the bone beneath the site of the exostoses are among the most interesting features of this condition of the skeleton. Many explanations have been advanced to account for these peculiarities, most of them relating the conditions either to a generalized disease, such as rickets, syphilis or tuberculosis, acting on the epiphyseal line or to a failure of the metaphysis to become modeled into a normal shaft because of some inherent and hereditary defect. The first group of explanations relating to the epiphyseal line and originating with Virchow have been gradually abandoned. The other group of explanations relating to the metaphysis are more current but are mostly theoretical without a true pathologic or embryologic basis.

Another of the more intriguing deformities is the stunting of the growth of those bones that do not bear direct strain or weight, such

as the ulna and fibula. The curious way in which these two bones are outstripped in size and growth by their neighbors, the radius and tibia, affords an important clue to the pathologic picture of the disease.

Microscopically, the duplication in the multiple exostoses of the histologic picture, described under single osteochondromas, indicates that the histogenic processes described in connection with those lesions also apply to the more diffuse form of this skeletal condition.

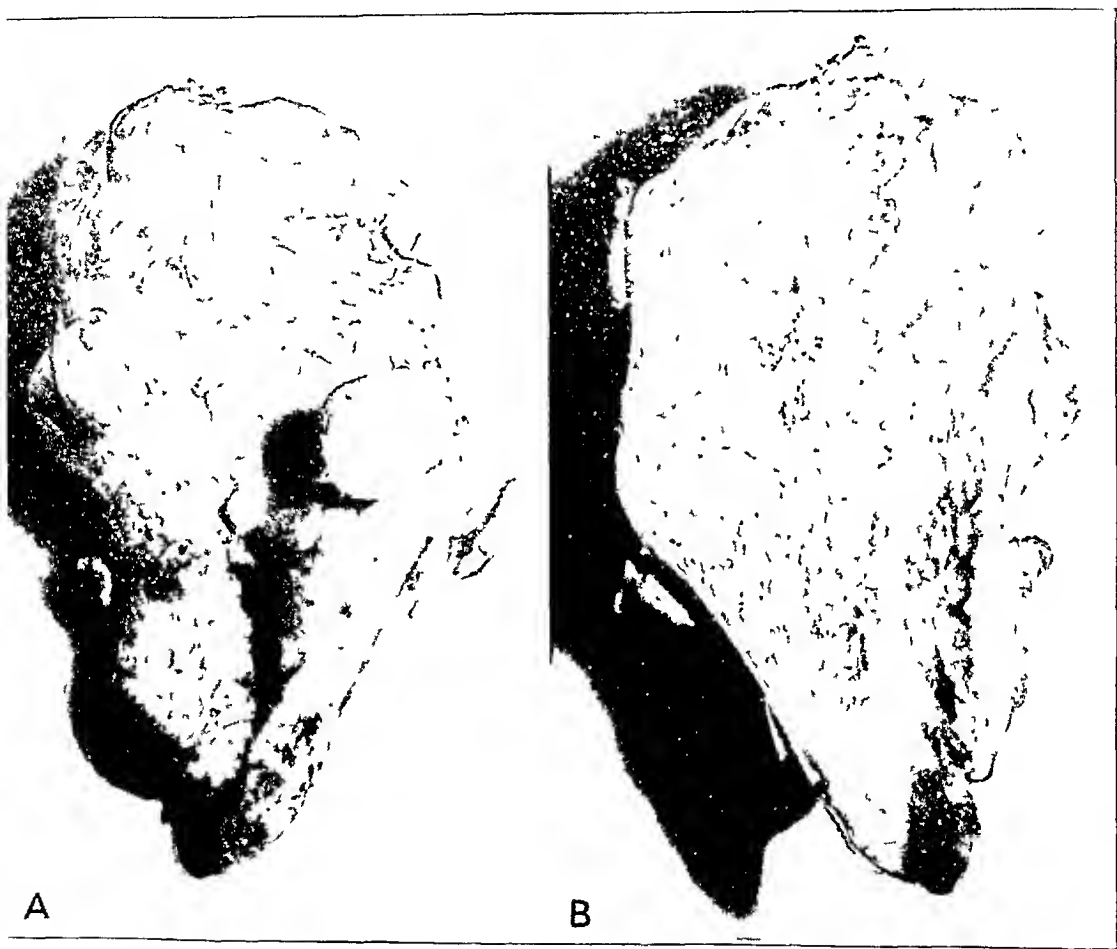


Fig. 26 (P. N. 19339).—Gross specimen from a case of hereditary, deforming chondrodysplasia after a resection of the upper end of the tibia and upper end of the fibula. The uncut surface (A) shows the numerous cartilaginous outgrowths and synostosis between the fibula and tibia. The cut surface (B) shows islands of chondromatous tissue extending into the epiphyseal and metaphyseal regions of the cancellous bone.

HISTOGENESIS

The formation of single exostoses as an exaggeration of a normal bony protuberance when maladjustment occurs between the periosteal cuff and the precartilaginous connective tissue embedded in the end

of the tendon suggests that in the condition of hereditary deforming chondrodysplasia, in which so many of these tumors are present, a similar disturbance affecting the periosteum and the precartilaginous connective tissue is present. In its earliest state, the bulk of the periosteum is in reality perichondrium, a tissue identical with the precartilaginous connective tissue which persists about the joints and in the ends of the tendons. It is clear, therefore, that if there is an arrest of development and a tendency for this precartilaginous tissue to persist not only in periarticular regions but also at points in the periosteum, the bones of cartilaginous origin will be affected throughout. This probably occurs in multiple exostoses. Not only do the periarticular points of primitive connective tissue act as sources for these cartilaginous growths, but, in addition, the periosteum at many points does not develop as such but is replaced by insufficient amounts of the more primitive perichondrium.

The failure of the periosteum to develop adequately, or rather its tendency to lag behind its normal rate of differentiation, has a multiplicity of effects on the bone beneath. Among other things, the cortex does not achieve its full thickness, owing to the absence of an adequate subperiosteal layer of osteogenic tissue provided with fully developed osteoblasts. In addition, the envelop formed by the periosteum is insufficient and incomplete, resulting in a failure of the periosteum to act as an efficient limiting membrane to growth of bone. Failure in this function as a limiting membrane leads to widening of the metaphysis and irregular protrusions through points of defect in the periosteum. The inadequacy of this line of limitation is most apparent in the fibula and ulna. In view of Wolff's¹² law, which states that the development of bone structure is in accordance with bone stress and strain, it is important to bear in mind that these accessory bones of the forearm and foreleg are not subjected to the direct stress received by the radius and tibia and therefore lack the corrective influence of their neighbors. As a result, the defects brought about by periosteal deficiency are accentuated.

The formation of exostoses akin to those found in cases of single osteochondroma are to be ascribed to the precartilaginous tissue in the tendon ends which does not form its destined junction with an outgrowing periosteal cuff. The irregular masses of cartilage found next to the cortex and growing inwardly are more likely due to persisting strands of primitive perichondrium. The entire process is extremely complicated, but it shows what a fine state of balance among various tissues of similar functions is necessary to produce the normal.

12. Wolff, J.: Ueber die inneren Architectur der Knochen und ihre Bedeutung für die Frage vom Knochen Wachstum, *Arch. f. path. Anat.* 1:389, 1870.

PROGNOSIS AND TREATMENT

The prognosis for life in these cases is good, but there is no adequate form of treatment except operation for correction of deformities after the growth period has ceased. Most of the deformities, such as shortening of stature and unequal length of the bones of the extremities, usually give no indication for treatment, but exostoses causing neurologic manifestations, dysfunction in the use of limbs or injury to vessels should be promptly excised.

In two cases in this series secondary malignant change occurred in these cartilaginous growths resulting in death from chondromyxosarcomas. Other such cases with malignant change have been reported from time to time in the literature. The treatment of such sarcomatous growths is discussed in the chapter on secondary chondromyxosarcoma.

CHONDROMAS OR CHONDROMYXOMAS

A fairly common type of cartilaginous tumor, designated here as benign chondroma, resembles the exostoses histologically, but has not the same periosteal location or the same preponderantly osseous structure that is characteristic of the base or pedicle of the osteochondromas.

The typical chondroma is a benign lesion occurring in the small bones of the hands and feet or about the ribs and spine in patients between the ages of 20 and 30. In the phalanges of the hand where this tumor is most frequently located, the growth produces a central area of rarefaction in the affected bone which in the roentgenogram is visible as an expanded and cystic area within a shell of cortical bone. These chondromyxomas have been described as occurring commonly in the long pipe bones and about the pelvis in either a central or a periosteal location. However, in such locations these tumors are rarely of central origin, and of those of periosteal origin described as chondromas the majority are in reality osteochondromas with a large cartilaginous cap; they have been grouped under the exostoses in this paper (table 1). It is also essential to point out here that many of the chondromas growing to tremendous size, described as benign lesions in the literature, are essentially slowly growing chondromyxosarcomas arising secondarily in benign exostoses. This type of tumor is subsequently discussed in this paper under the heading of "secondary chondromyxosarcoma."

CLINICAL FEATURES

In the present series of seventy-one chondromyxomas (tables 2 and 3), males and females were about equally affected; the majority of the patients were white, and only two such lesions were recorded in Negroes. The curve of age distribution is shown in figure 27 and resembles the benign osteochondromas except that the peak of incidence is a decade later, between 20 and 30 instead of 10 and 20 years. The

predominant location, as shown in figure 28, is in the bones of the hands and feet, fifty of seventy-one lesions occurring in such localities. The ribs about the sternum in the region of the costochondral junction are next in order of frequency of involvement, and the region of the spine is also a common site.

The patient affected with a benign chondroma or chondromyxoma is most often an adult, who complains of recurrent soreness in a tumor of stationary or slowly increasing size located in one of the phalanges of the hand or foot. The symptoms are usually mild and protracted,

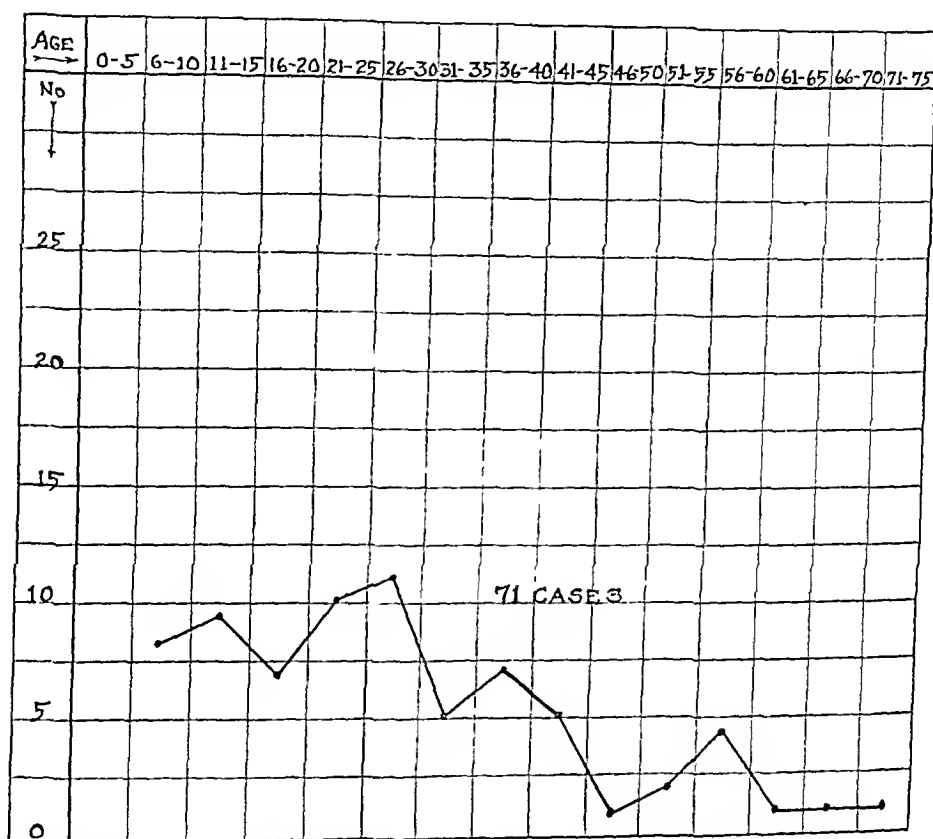


Fig. 27.—Chart showing age incidence of benign chondromas occurring in the small and large bones of the skeleton.

the clinical course extending on an average of over five years. Trauma is often recalled in connection with the initial appearance of the tumor and also again in connection with the exacerbation of the symptoms which brings the patient to the physician. Neither pain nor swelling is severe, the size of the tumor being in most instances less in diameter than a ten cent piece. Multiple involvement is not as frequent as one might infer from the literature. In the present series, only four cases of multiple chondromas are recorded, and in every one of these instances the diffuse involvement was in the hand or foot. However, in addition to the nodules, varying from three to ten in the small bones, there was in two of these cases an involvement of a long bone (femur or humerus).

The results of physical examination are usually negative, except for the local changes in the area of the tumor. Evidences of specific infections such as syphilis and tuberculosis have not been recorded, nor has bursitis been present in this series. The skin is usually unchanged, and the soft parts are freely movable over the tumor, which is firm to palpation, smooth or lobulated to the touch and securely attached to the adjoining bone. Pathologic fracture is present in 10 per cent of the lesions.

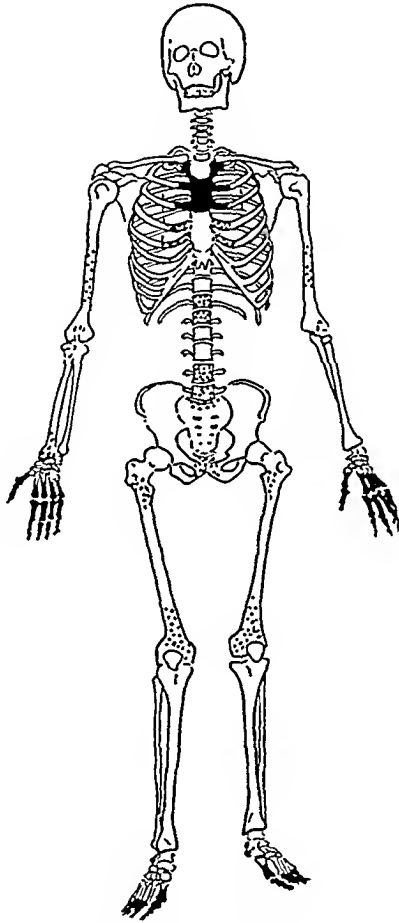


Fig. 28.—Incidence of chondromas according to skeletal location. The solid black areas indicate the most frequent sites; the dotted areas, the points occasionally involved.

About the ribs and sternum or when occurring centrally in the long bones, these growths may be of considerable dimensions and larger than an adult fist (fig. 29). In these larger growths a sudden increase in size or malignant change is far more frequent than in the small bones, and recurrence after a primary operation far more likely. Malignant change seems prone to occur in these larger tumors, particularly when they are associated with multiple chondromas in the small bones such as in the two cases just mentioned.

TABLE 2.—*Benign Chondromyxomas in Small Bones of the Hands and Feet*

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
45163	W	F	13	Multiple fingers and toes	Con- genital	Tumor	Multiple rarefied areas	Excision, 1929	Myxoma; cartilage; bone	Discharged well
40421	W	F	30	Phalanx, ring finger	..	Tumor	Curetted, 1929	Discharged well
39758	W	F	10	Phalanx, right little toe	2	Tumor; pain	Central rarefied area	Curetted, 1927	New bone fetal cartilage	Discharged well
39538	W	F	39	Phalanx, right thumb	..	Pathologic fracture	Central expanded rarefied area	Curetted, 1927
33169	W	F	18	Phalanx, right little finger	72	Trauma; tumor	Curetted, 1925	Cancellous bone; adult cartilage	Discharged well
37112	W	F	30	Metacarpal, right	48	Fracture; tumor	Resection, 1925	Fetal cartilage; myxoma	Well 5 yr.
36660	W	F	32	Phalanx, middle finger	60	Trauma; tumor; pain	Central and cortical rarefied area	Curetted, 1925	Adult and calcifying cartilage	Well 4 yr.
36658	W	F	13	Phalanx, right forefinger	56	Trauma; tumor; pain	Central expanded rarefied area	Curetted, 1925	Cancellous bone; adult cartilage below myxoma	Well 4 yr.
36005	W	F	19	Phalanx, right finger	72	Trauma with repeated fracture	Rarefied area with fracture	Irradiated, 1924; operation	Well 6 yr.
35942	W	M	46	Thumb, right	24	Trauma with dislocation	Ossified tumor in tendon	Excision, 1925	Discharged well
35398	W	F	29	Middle phalanx, thumb	..	Pathologic fracture	Translucent area with ossification	Roentgen therapy, 1924	Healing after 2 yr.
35501	W	M	9	Thumb and forefinger, left	36	Trauma	Multiple periosteal and central translucent tumors	Unchanged 6 yr. after
35308	W	M	19	Metacarpal, little finger	..	Tumor	Central rarefied area	Irradiation, 1924	Some improvement 6 mo. later
35263	W	M	37	Phalanx, index finger	1½	Trauma; pain	Central expanded rarefied area	Amputation, 1924	Discharged well
34886	W	F	12	Phalanx, ring finger	24	Tumor	Central rarefied area	Observed, 1923; no operation	Well 7 yr.
34058	W	F	40	Finger, left middle	..	Tumor	Central rarefied area	Excision, 1923	New bone; adult cartilage	Well 7 yr.
33152	W	F	12	Phalanx, ring finger	12	Tumor	Central and cortical rarefied area	Irradiation, 1922	Unimproved; lost
33071	W	M	23	Phalanx, toe	¼	Trauma; tumor	Central expanded rarefied area	Amputation, 1923	Fetal cartilage; myxoma; new bone	Well 6 yr.
32848	W	M	11	Great toe	..	Tumor	Sesamoid bone
32763	W	M	11	Phalanx, middle finger	24	Trauma; tumor; pain	Central expanded rarefied area	Curetted, 1923	Well 6 yr.
32026	W	M	6	Phalanx, fourth finger, right	24	Tumor	Central and periosteal trans- lucent area	Excision, 1922	Dense myxoma; fetal cartilage	Discharged well

20872	W	F	..	Phalanx, index finger	18	Tumor; pain	Sesamoid bone (?)	No operation; observed, 1922	Well 8 yr.
20617	W	M	30	Phalanx, thumb	24	Trauma; tumor	Central rarefied area	No operation; observed, 1922	Unchanged
20604	W	F	35	Phalanx, ring finger	168	Trauma; pain	Central rarefied area	No operation; observed, 1922	Well 6 mo.; lost
20326	W	F	31	Phalanx, forefinger	96	Trauma; tumor; pain	Central rarefied area	No operation	Unchanged
20245	W	F	10	Fifth, metacarpal	36	Trauma; tumor; pain	Central rarefied area	Curetted, 1921	Well 6 yr.
20239	W	F	30	Phalanx, thumb	..	Tumor	Central rarefied area, cortex roughened	Amputation, 1921	Well 8 yr.
20010	O	M	10	Phalanx, big toe	3	Tumor	Central expanded rarefied area	Amputation, 1921	Well 7 yr.
28164	W	M	23	Phalanx, index finger	60	Tumor	Central rarefied area	Curetted, 1921	Well 9 yr.
28365	W	M	27	Third, metacarpal	84	Heel fracture	Central expanded rarefied area	Curetted, 1921	Well 9 yr.
27696	W	F	42	Phalanx, ring finger	24	Pain; tumor	Periosteal translucent area	Excision, 1921	Discharged well
26622	W	M	39	Phalanx	48	Trauma; tumor; pain	Periosteal translucent area	Excision, 1920	Well 9 yr.
26259	W	F	75	Phalanx, little finger	48	Tumor	Central expanded rarefied area	Amputation, 1920	Well 8 yr.; dead 1928, heart disease
25616½	W	M	70	Third metacarpal	..	Limitation of motion	Multiple rarefied areas	Amputation	Discharged well
25254	W	M	23	Phalanx, third toe, left	1½	Trauma with radiologic fracture	Central expanded rarefied area	Amputation, 1918	Well 1 yr.; lost
23886	W	M	35	Phalanx, little finger	48	Trauma; tumor; pain	Periosteal translucent area	Excision, 1918	Discharged well
20044	W	F	25	Phalanx, ring finger	12	Tumor	Central expanded rarefied area	Curetted, 1919	Discharged well
16554	W	M	32	Metacarpal, middle finger	168	Trauma; tumor	Periosteal translucent area; new bone	Excision, 1921	Well 10 yr.
15597	W	M	62	Phalanx, ring finger	240	Trauma; tumor	Amputation, 1914	Well 14 yr.
14552	W	F	15	Third metacarpal	12	Trauma; tumor	Central rarefied area	Resection, 1912; excision, 1913	Well 5 yr. after recurrence
12206	W	F	30	Phalanx, index finger	336	Trauma; tumor	Curetted, 1911	Discharged well
8630	W	F	23	Phalanx, little finger	60	Tumor	Excision, 1907	Well 13 yr.
6892	W	F	40	Phalanx, middle finger	12	Tumor	Amputation, 1901	Well 3 yr.; lost, 1930
6530½	W	F	24	Phalanx, ring finger	..	Tumor	Excision	Discharged well
730	W	M	58	Phalanx, toe	324	Trauma; tumor	Amputation, 1890	Discharged well

TABLE 3.—Benign Chondromas in Large Bones

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
38196	W	M	19	Os calcis	60	Pain; tumor	Small rarefied areas	Curetted, 1926	Well 4 yr.
42985	O	F	8	Radius, styloid	..	Tumor	Excision, 1925	Cartilage in tendon	Discharged well
41435	W	M	24	Rib	..	Tumor	Excision, 1927	Adult cartilage	Discharged well
37746	W	M	25	Os calcis	1/2	Trauma; tumor; discharging sinus	Drained, 1926; amputation advised	Unimproved
40657	W	M	14	Vertebra	..	Tumor	Excision, 1927	Cartilage	Discharged well
35908	W	F	19	Symphysis pubis	108	Trauma; tumor	Central destruction of bone	Irradiation, 1927	Lost
38931	W	F	26	Sternoclavicular joint	150	Tumor; pain	Excision, 1926	Hypertrophied joint cartilage	Discharged well
38062	W	M	10	Rib, second, left	120	Trauma; tumor	Cystic periosteal shadow	Irradiation, 1926	Well 4 yr., 1930
36808	W	M	7	Femur, left, lower	12	Pathologic fracture, twice	Subcortical rarefied area with fracture	Osteotomy; amputation, 1923	Joint cartilage; bone	Lost, 1925
34502	W	M	55	Sacrum and lumbar vertebra	180	Trauma; pain; tumor	Lobulated mass	Coccyx resected	Myxoma; cartilage
32482	W	M	43	Sternum	132	Trauma; tumor	Central expanded rarefied area	Observed, 1915; roentgen therapy prescribed	Signs of malignant change, 1930
32415	W	M	22	Humerus, shaft, left, pathologic	48	Pain; tumor	Central expanded rarefied area, roughened	Amputation, 1923	Connellous bone; fetal cartilage	Discharged well
30173	W	M	15	First lumbar vertebra	24	Pain	Periosteal translucent area	Excision, 1915	Cancellous bone; adult cartilage	Well 7 yr.
29814	W	F	16	Ribs, third and fourth	30	Tumor	Rarefied area	Observed, 1922; no operation	Well 8 yr.
26287	W	F	40	Humerus, upper, left	12	Tumor	Excision, 6 times, 1915 to 1919; amputation, 1920	Chondroma; adult cartilage	Recurred, well 10 yr. after
22017	W	F	30	Rib, third, sternal end	..	Tumor	Excision, 1918	Adult cartilage	Discharged well
22016	W	F	51	Femur, lower	84	Tumor; pain	Subcortical expanded rarefied area	Excision, 1917	Adult cartilage; hyalinized fibrous tissue	Well 6 yr., lost, 1930
10545	W	M	43	Os calcis	12	Pain; tumor	Central rarefied area	Curetting, 1916; amputation, 1919	Recurred, well 6 yr. after
18751	W	M	51	Ninth dorsal vertebra	12	Pain	Excision, 1915 and 1916	Cancellous bone; adult cartilage	Dead; second operation
17112	W	F	14	Rib	..	Tumor	Excision, 1913, twice; excision, 1914; treated by radium	Adult cartilage; new bone	Well 8 yr.; dead of tuberculosis
15395	W	M	49	Sternum, upper	36	Tumor	Partial excision, 1914	Well, 1923
13790	W	M	14	Ulna, head	4	Tumor; pain; stiffness	Translucent periosteal mass	Excision, 1913	Adult and calcified cartilage; myxoma	Well 9 yr.
11312	W	M	20	Thigh	48	Tumor; pain	Translucent soft part; shadow	Excision, 1911	Adult cartilage; laminated bone	Well 11 yr.
10167	W	F	24	Ribs, third, right	12	Tumor; pain	Translucent expanded area	No operation
8192	W	M	35	Fifth rib	..	Tumor	Excision, 1908	Recurred
8111	W	M	53	Os calcis, right	36	Tumor	Excision, 1907	Adult cartilage; myxoma	Recurred in 1 yr.
4093	W	M	70	Humerus, upper	13	Trauma; tumor; fracture	Amputation, 1895	Adult; total cartilage; myxoma	Dead, other causes 13 yr. later

ROENTGENOLOGIC FEATURES

In the roentgenogram a typical chondroma is a small, translucent and rarefied area occurring centrally in the shaft of a small bone. The cortex about the lesion is thinned and expanded, inviting pathologic fracture. Unlike the osteochondromas, neither new bone formation nor calcification is marked in these small lesions, although trabeculae traversing the tumor (composed of hyalinized fibrous tissue) may be

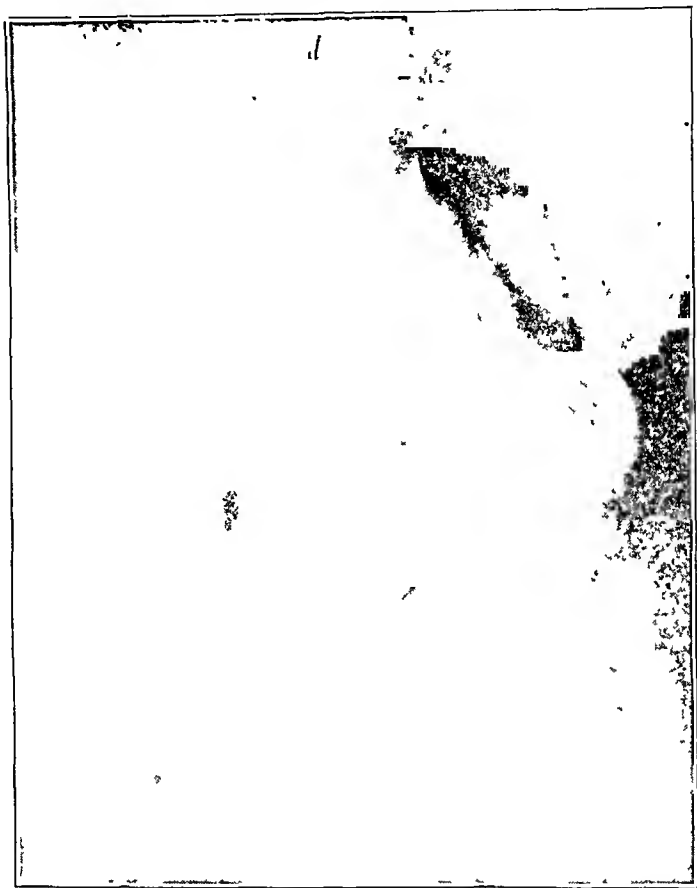


Fig. 29 (P. N. 32482).—A large chondroma of the sternum present for over fifteen years in a white man, aged 43. This tumor was first observed in 1915, and roentgen therapy was prescribed. Roentgenograms of this lesion are shown in figure 32. Despite repeated irradiations, the most recent x-ray films depict a change suggestive of malignancy.

visible in the x-ray film. Perforation of the bone shell with extension of a translucent shadow into the soft parts is not rare (fig. 30).

The benign chondroma is the most frequent lesion producing a central area of bone destruction in a phalanx. Bone cysts and giant cell tumors, which may occur in the small bones of the hands and feet and produce a similar picture in the roentgenogram, are more common in the metacarpal and metatarsal bones and are rarer in the phalanges. It is also helpful to bear in mind that multiple giant cell tumors or bone

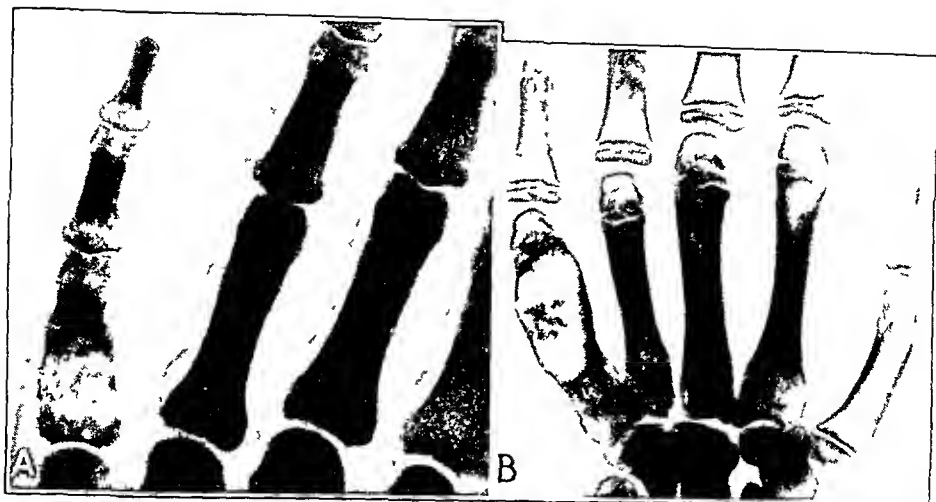


Fig. 30.—*A* (P. N. 29326) shows a central chondroma in the phalanx of the forefinger in a woman 31 years old. The appearance of this tumor followed trauma eight years previously. The cortical bone is intact, and the periosteal zones are not involved. *B* (P. N. 29245) shows a central chondroma occurring in a metacarpal bone in a girl, aged 10. This lesion also followed trauma three years previously, but was effectively treated with curetting and has remained well over six years.



Fig. 31 (P. N. 35336).—A roentgenogram showing the multiple punched-out areas due to gout occurring in the hand of a white man over 50 years of age. Other joints in the body were affected, and recurrent attacks of acute arthritis were present.

cysts are practically unknown in the small bones of the extremities. However, multiple punched-out areas of bone destruction which are not encapsulated by a shell of cortical bone in these localities may be produced by gout (fig. 31). Metastatic carcinoma and multiple myeloma practically never affect these small bones, unless the rest of the entire skeleton is riddled with the disease.

The majority of the larger tumors of the chondroma class are situated about the sternum at the costal chondral junctions or within the body of this bone. In this location they produce a gnarled mass of rubbery consistency which is difficult, because of its location, to visualize



Fig. 32 (P. N. 32482).—*A* shows the central chondroma of the sternum shown in figure 26. The roentgenogram was made eight years after the first observation, and although the lesion has grown the bone shell is still intact and the tumor is outlined by a definite calcified margin. *B* shows the same lesion five years later. Note the spotting and beginning granular appearance of the lesion and the extension beyond the bone shell. Because of the spotting and the hazy margins of the growth, this picture is suggestive of an early malignant change. Such a malignant change is very common in chondromas of the large bones after they have persisted for many years in a benign state.

clearly in the roentgenogram. The diagnosis, however, can usually be made from the location of the lesion and by the expansion of the bone which occasions no great amount of destruction or erosion. The absence of an infiltrating shadow in the periosteal zones is against the presence of malignancy in these cases (fig. 32).

True central chondromas of the long bones are extremely rare, and it is doubtful whether such a diagnosis is justified on the basis of the roentgenogram alone. In nearly 2,000 tumors of the bone there are but 5 well established cases, and in these, the resemblance is so close to malignancy in the x-ray film, and the tendency for the lesion to recur and to be cured only by radical operation is so great that there is little practical harm in classing these tumors as forms of chondrosarcoma,

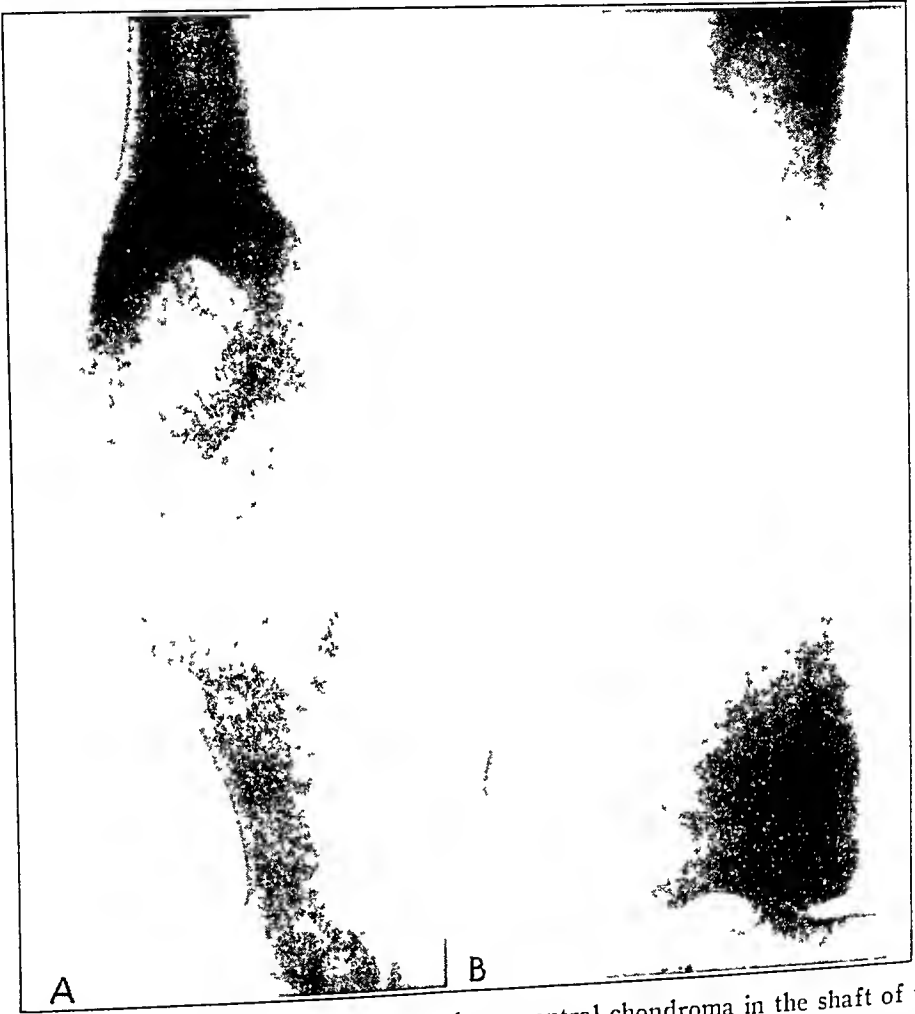


Fig. 33.—*A* (P. N. 32415) shows a large central chondroma in the shaft of the humerus. The symmetrical nature of the expansion resembles a benign bone cyst, but the multilocular markings of the cavity and the peculiar roughness extending beyond the shell of cortical bone suggest a central chondroma which is extremely rare in the long bones. *B* (P. N. 22016) shows a rare central chondroma occurring in the epiphysis of the lower end of the femur. This resembles somewhat in appearance a benign giant cell tumor, but it has again the characteristic multilocular appearance of a chondroma. This is also a rare type of lesion in this location.

although those not experienced may be misled into an erroneous diagnosis of cyst of the bone. Nevertheless, from a scientific standpoint, the possibility of the occurrence of a true central chondroma in the long

bones must be conceded, and I have reproduced the illustrations of the roentgenograms of several of these cases as more or less of a curiosity. The only distinctive roentgen features are the tendency to expand the bone, the marking of the translucent areas by lines and particles of calcification which produce a distinctly multiloculated effect and the involvement of the periosteal region by peculiar roughened areas escaping beyond the cortex (fig. 33).

GROSS PATHIOLOGY

The outstanding characteristics in the gross specimens of neoplasms composed primarily of cartilage are the lobulated and gelatinous character of the growth. The tumor is always composed of numerous pockets, marked off by visible fibrous trabeculae, and within these pockets there is a typical translucent and congealed substance of more or less rubbery consistency, which under the microscope can be identified as cartilage. Variation in this lobulated and gelatinous appearance depends on the size of the tumor. In the small bones, the capsule containing osseous material lends a firmness to the tumor, and in addition, calcification may aid in solidifying the mass. Elsewhere in the large bones where the tumor attains a greater size, there is a tendency to cystic change in the pockets of the lobules, and these cysts may contain a syrupy fluid which pours from the tumor when it is sectioned (fig. 34).

The color of the tumor varies from a pearly gray to light yellow. Occasionally small foci of hemorrhage may discolor the tumor with deep red or black. However, these growths are not vascular, and the vessels described in the literature, particularly under the old terminology of angiochondroma, are to be found in the adjacent soft parts and not in the tumor proper.

In the small bones the structure of the chondroma is fairly characteristic. In most instances the bone is intact (fig. 35), and portions of the cancellous bone usually remain in one or more areas, either forming the boundary of the tumor at one end or projecting into the tumor at one or more points as the remains of the original medullary structure. Within such bony confines the gelatinous mass infiltrates everywhere as if it had been poured into a mold and left there to congeal and harden. Within the congealed substance, a few gritty areas of calcification may be felt.

About the ribs or spine these growths are firm, nodular masses which become cystic when attaining to large size. In the rare instances in which these tumors involve a long bone, they show greater proliferative powers, and the original mass is reduplicated by similar clusters of lobules. Some of these reduplicated masses may be uniformly gelatinous, others are cystic and exude fluid from their smaller pockets. These

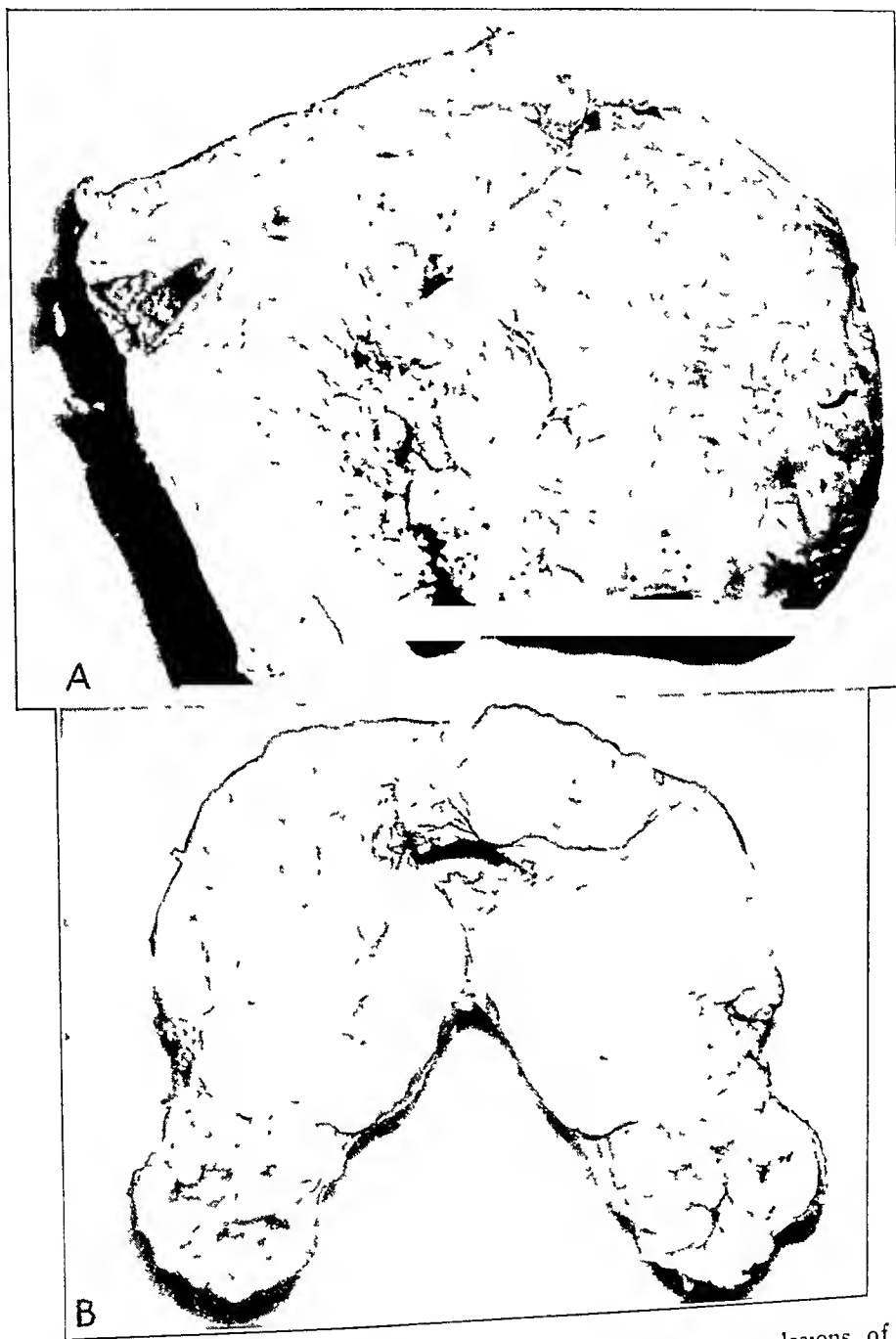


Fig 34—Gross specimens of two recurrent chondromatous lesions of the large bones in patients who have remained well for over five years. *A* (P. N 26287) shows a lobulated tumor mass from a central chondroma of the upper end of the humerus, and *B* (P. N 25766) a similar tumor mass with cystic changes associated with an exostosis in the lower end of the femur. These lesions illustrate the prognostic paradox in benign chondromas. The chondromas in the large bones, although typically benign under the microscope, have a decided tendency to recur and undergo malignant change, whereas chondromyxomas of the small bones, although resembling a malignant condition under the microscope, are clinically benign.

larger tumors of the benign chondroma class are difficult to distinguish in the gross (or even under the microscope) from chondromyxosarcomas, and because of their clinical behavior must be looked on as potentially malignant.



Fig. 35 (P. N. 33071).—Low magnification of a central chondroma occurring in the terminal phalanx of a toe. The lobulated tumor mass is encapsulated by a thin shell of bone.

MICROSCOPIC FEATURES

The bulk of the benign chondroma is composed of fairly normal adult cartilage. Under the microscope, this chondral substance shows a matrix of hyaline material divided into lobules by acellular strands of

eosin-staining connective tissue. The cartilage cells lie in pairs or tetrads, in small lacunae, and the nuclei, which readily undergo pyknosis, are surrounded by a generous amount of eosin-staining cytoplasm.

Variations of this typical structure depend on the location of the tumor. About the ribs and spine, the hyaline substance is much increased, the lobules are larger with fewer strands of connective tissue and the cartilage cells are sparse. This type of chondroma resembles



Fig. 36 (P. N. 22016).—Photomicrograph of a chondroma in a large bone. The cellular connective tissue from which the chondroma is derived is shown at the margin overlying the tumor proper. The lobulated areas of adult cartilage are shown below. Note the sparsity of cellular material and the large amount of hyaline substance.

in its structure normal joint cartilage, and in all probability some of these tumors are hypertrophied and distorted masses from the costochondral junction (fig. 36) or vertebral disks.

In the rare instances of large chondromas in the long bones, necrosis and spotty calcification in the cartilage may be found. Connective tissue

cells are more frequent in the strands which mark off the lobules, and occasional islands of hyaline material in which fetal instead of adult cartilage cells are found are more likely to be seen (fig. 37).

In the small bones, the microscopic picture is changed by the manner in which the capsule infiltrates from the margin. Here there is much cellular connective tissue and fetal cartilage intermingled to form typical myxoma. In addition, the connective tissue at the margin of these



Fig. 37 (P. N. 38666).—Photomicrograph of a cellular area at the margin of a chondroma of a large bone. Numerous spindle cells are present in the connective tissue, and many of the cartilage cells are of the fetal type. An area of spotty calcification is seen. This lesion was in a white woman, aged 37, who had two unsuccessful curettings followed by amputation. The patient is living four years after the first operation. This picture demonstrates the borderline type of chondroma in which the exact onset or presence of malignant transformation cannot be determined. Clinically, the lesion has been tabulated with chondromyxosarcoma arising secondarily in a benign chondroma.

tumors, which gives rise to such myxoma, shows definite ossification with the formation of islands of new bone. This transition from cellular connective tissue to myxoma to cartilage with a parallel production of

new bone is more typical of chondromyxosarcoma. In fact, if it were not for the location of these tumors in the small bones and their encapsulation, the diagnosis of benign chondroma or benign chondro-

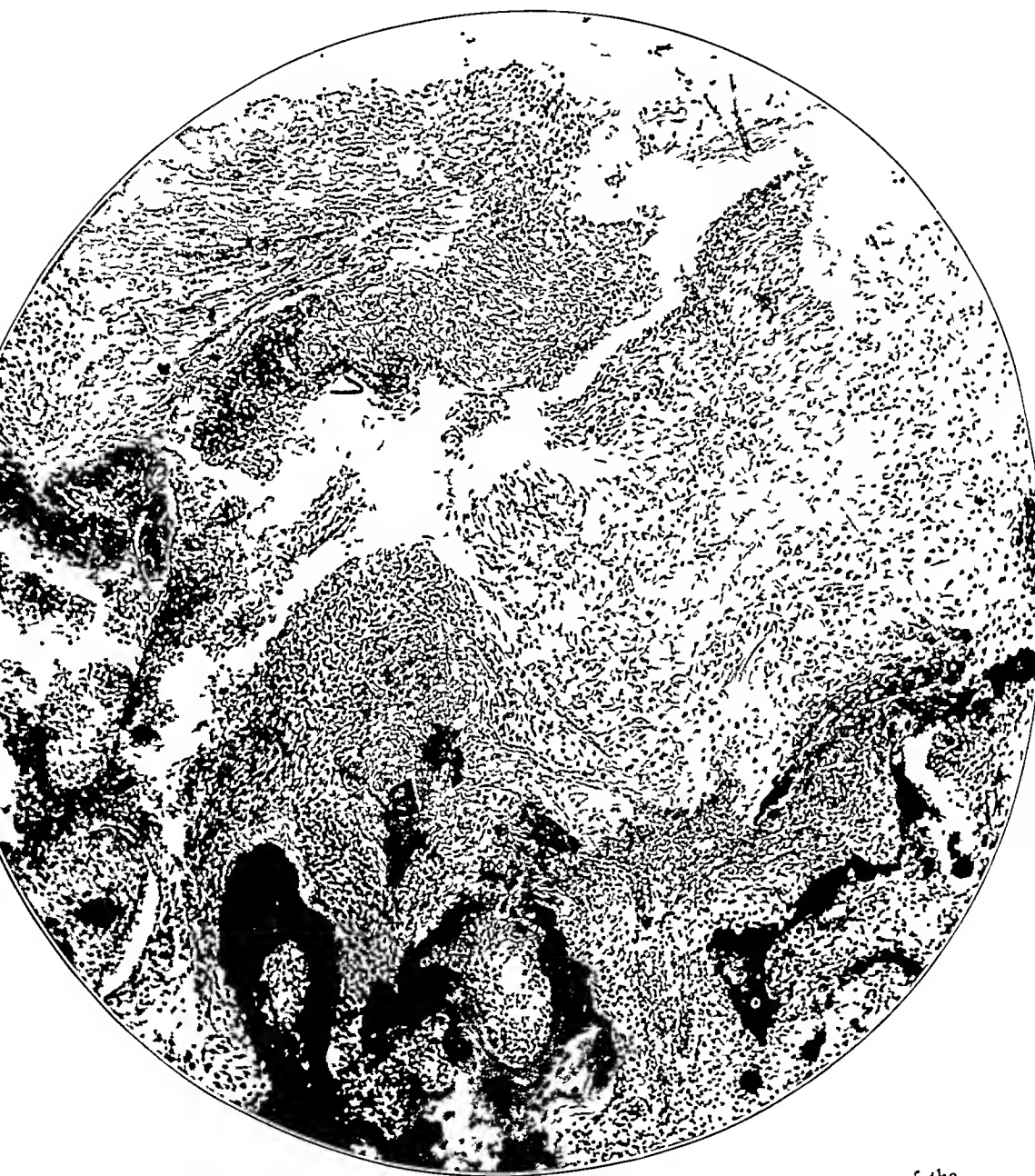


Fig. 38 (P. N. 23886).—Photomicrograph of a central chondromyxoma of the small bones showing the more cellular areas which are responsible for the origin of the tumor. Dense strands of connective tissue can be seen giving rise to fetal and adult cartilage cells. Cartilage is undergoing calcification at one point.

myxoma from a microscopic standpoint would have to be changed to that of sarcoma (fig. 38). But in this respect the microscopic picture in these cartilaginous growths is misleading, since the tumors of this

type in the small bones of the hands and feet are, on the basis of clinical evidence, uniformly benign, while the chondromas in the larger bones (sternum, ribs, long bones, etc.) are potentially malignant despite a more benign histologic appearance.

When a large group of tumors of the benign chondroma class is reviewed microscopically in connection with the sections of many cases of exostosis and also many cases of chondromyxosarcoma, it can be seen that these tumors as a group represent a borderline or transition between the osteochondromas, on the one hand, and the chondromyxosarcomas, on the other.

All of these tumors show the same transition from cellular connective tissue to myxoma with fetal cartilage to adult cartilage with a parallel formation of new bone from connective tissue. In benign osteochondromas, the bone formation predominates, the cartilage is adult cartilage, and strands of active connective tissue and myxoma can be located only as insignificant remnants in the capsule of the tumor by the use of the high power of the microscope. In the benign chondromas, adult cartilage and not bone predominates. In the strands of connective tissue which divide the chondroma into lobules, myxoma and fetal cartilage is nearly always absent, but in the strands of connective tissue which form the capsule, this tissue is easily found. Particularly in the small bones is fetal cartilage a common occurrence, and myxomatous areas along with new bone formation are the rule in the margin of these small growths. In chondromyxosarcoma, the cellular strands of connective tissue giving rise to myxoma with fetal cartilage infiltrate everywhere, and islands of abortive cartilage with malignant nuclei of the vesicular type are replaced at intervals by areas of new bone formation.

A graded series of histogenic changes in these tumors can thus be traced, the amount and degree of cellular activity in the primitive connective tissue, which is the mother substance of these growths, indicating in a general way the degree of the malignancy.

HISTOGENESIS

Most of the chondromas and chondromyxomas represent histogenetically supernumerary joint cartilages. In the regions in which they predominate—the hands and feet, the spine, ribs and sternum—there are far more joints and articular surfaces than elsewhere in the body. Embryologically, these joints are laid down by strands of primitive precartilaginous connective tissue which cut across the axis of the future bones at right angles (fig. 39). These precartilaginous strands are the same type of primitive connective tissue that forms the osseous ends of tendons and gives rise to the abnormalities of exostoses and osteochondromas. This accounts for the similarity histologically between the chondromas and the exostoses. In forming the joints, this pre-

cartilaginous tissue normally undergoes mucoid regressive changes to form the synovial lined joint cavities. However, aberrant persisting strands which do not thus regress are responsible at a later date for the origin of cartilaginous islands in the bone which form the chondromas and chondromyxomas. It is for this reason that the chondromas are found most frequently in a central location in bones in the regions of the body where there are the greatest number of joints.

The persistence of such precartilaginous tissue about the joints, particularly at the point of reflexion of the joint capsule may be demonstrated in normal adults (figs. 13 and 14). Neoplastic tendencies in

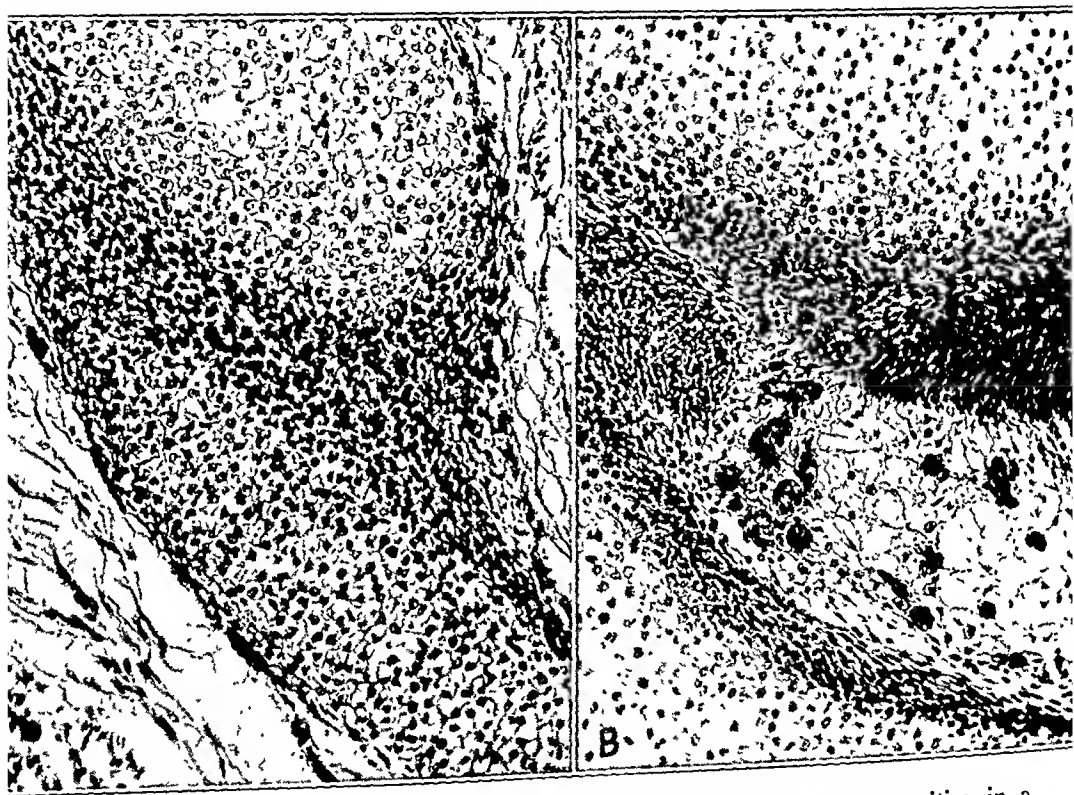


Fig. 39.—Photomicrographs showing the development of joint cavities in a human embryo 14 cm. in length. At *A*, the dense strands of embryonic connective tissue are cutting across the axis of the bone which is preformed in cartilage at the site of the future joint cavity. At *B*, this dense connective tissue is undergoing mucoid regression to form the joint cavity, and the capillaries of the future synovia are forming.

such tissue are shown in cases of osteochondromatosis of the knee joint (fig. 19), and the potentialities for continued growth are indicated in the chondro-osseous nodules formed in these regions in chronic infectious arthritis. The most conclusive evidence, however, is the appearance in these chondromatous tumors of so-called pure myxoma tissue, which is a histologic duplication of the regressive mucoid changes observed in the embryo during the formation of the joint cavities. This

myxomatous character is particularly prominent in the chondromas of the small bones and in those chondromatous lesions of the large bones undergoing secondary malignant change (fig. 66).

From a practical point of view, it is of importance to understand, if possible, why the chondromas should present a more cellular and myxomatous appearance when they occur in the small bones and yet remain in this location so uniformly benign; and why, on the other hand they should be more predominantly cartilaginous when occurring in the long bones and yet more prone to malignant change. The explanation is to be found in the capsular changes. In the small bones, the cartilaginous center of the tumor never extends far from the influence of the cortical and periosteal margin of the growth, owing to the limitations of space. Thus the myxomatous strands characteristic of the margin of the chondromas are always readily visible among the cartilaginous areas. At the same time, normal periosteum with its subperiosteal osteogenic layers is capable of reacting to the tumor and laying down a protective shell of new bone (fig. 35), favoring a benign course in these smaller growths.

In the large bones, the conditions are reversed. The more central lobules of cartilage grow and reduplicate at some distance from the periosteal and capsular margin of the tumor. Cellular connective tissue strands and reactive new bone are therefore less likely to find their way into the chondral substance of the tumor. Therefore, within the chondroma, daughter lobules arise which are remote from the sphere of influence of cortical bone, and hence are more prone to sarcomatous change. For, from a study of various types of tumors of the bone (Geschickter and Copeland¹³), there is reason to believe that the potentialities for malignancy increase as the power of reaction in normal cortical bone decreases and its sphere of influence becomes remote.

PROGNOSIS AND TREATMENT

When these benign cartilaginous tumors are quiescent and give mild or no symptoms, they are best let alone and kept under observation by repeated roentgen examination. If because of their position they are frequently subjected to trauma, resulting in soreness and discomfort to the patient, their complete surgical removal should be undertaken, if this is feasible and the tumor is not too large. In the phalanges the lesion is usually small enough to permit preservation of the continuity of the bone after thorough curetting followed by cauterization. The case with which this tumor tissue is transplanted in the wound with resulting recurrence, however, should constantly be kept in mind.

13. Geschickter, C. F., and Copeland, M. M.: Tumors of the Bone, *Internat. S. Digest* 10:323 (Dec.) 1930.

Recurrence is not frequent following operation on chondromas in the small bones. Approximately one third of the cases in this series were treated by primary amputation or radical resection, and in all such cases a permanent cure was effected. When curettement is followed by adequate cauterization, either thermally or chemically with 50 per cent zinc chloride, permanent cures have been established in such lesions occurring in the bones of the hand or foot.

In the chondromas occurring in the large bones, recurrences have followed operation in approximately 25 per cent of the cases. In some of these instances the growth returned after repeated partial excisions when the neoplasms, because of location, could not be completely removed. It is important to record here that patients followed from five to ten years after the first observation have remained well without treatment, although in some instances, such as the case shown in figure 32, there has been a gradual increase in the size of the tumor and recent evidence of malignant change.

When a previously quiescent tumor shows sudden signs of increased growth, with an exacerbation of symptoms, immediate and complete removal is indicated, as secondary malignant change is to be expected. In the instances in which the patient has been so unfortunate as to neglect the growth and allow the tumor to become of unusual size, or in which the location about the sternum or spine makes complete removal difficult or dangerous, partial excision followed by radium therapy should be attempted. The clinical follow-ups on the malignant cases arising from previous benign tumors of this group warrant a trial of thorough irradiation by means of radium. A favorable prognosis can usually be given unless the tumor is of the type just discussed and is too large or in too vital a location to permit complete removal.

In deciding whether a particular lesion in this group is to be treated from the benign or malignant standpoint, the location and not the pathologic changes must be given primary consideration. Chondromas occurring in the small bones of the hand or foot (the os calcis excepted), regardless of their pathologic appearance, may be looked on as benign lesions, curable by thorough extirpation (curetting and cauterization). True chondromas of large size occurring about the sternum and spine or in the long bones, regardless of their microscopic appearance, must be looked on as potentially malignant, and their surgical removal, if indicated, should be followed by radium therapy.

PRIMARY CHONDROMYXOSARCOMA

There is a divergence of opinion in the literature concerning the relationship of simple exostoses and benign chondromas to sarcoma. Cases of so-called malignant degeneration in chondromatous tumors have been cited from time to time in the older literature and have been estimated as occurring in about 5 per cent of congenital exostoses.

More recently, Hyndman¹⁴ questioned such a conclusion and has stated that there "seems to be no evidence except possibly in a single instance, that any of the malignant changes (in the literature) are other than chondromatous or osteochondromatous." Bloodgood has been quoted in support of this statement.

There is possibly some room for doubt if attention is focused on the benign exostoses or chondromas and a search made among these lesions for instances in which secondary malignant change has resulted in metastases and death. Even from such a point of view there are undoubtedly cases in which death accompanied by generalized metastases has occurred, as will be demonstrated in the subsequent discussion of secondary chondromyxosarcoma. However, if one assumes an entirely different method of approach, beginning with an analysis of the various forms of osteogenic sarcoma, and seeks to determine on a histogenic basis whether or not sarcoma of such types is possible in the kind of neoplastic tissue responsible for exostoses and chondroma, the entire matter can be settled with little room for speculation or question.

The greatest number of tumors in the group of osteogenic sarcomas contain cartilage in association with a type of myxomatous connective tissue, indicative of a mode of origin analogous to the benign exostoses and chondromas (Geschickter¹⁵). As in the foregoing analysis of the benign lesions, this form of connective tissue can be traced to a survival at points in the skeleton of primitive perichondrium and periarticular strands of a similar precartilaginous tissue.

The relationship of these chondral forms of osteogenic sarcoma to the benign tumors of the fibrocartilaginous group is, therefore, an intimate one, and the true basis of origin among these various neoplasms is so nearly identical that it is often impossible, even with all the data at hand, to predict whether the outcome of the growth will be benign or malignant.

However, among these lesions there is a primary form of chondromyxosarcoma which shows from the start its sarcomatous bent. It is a very malignant tumor arising periosteally, which does not at the onset involve either the cortex or the medullary cavity of the bone (fig. 40), and which in the roentgenogram is characterized by its translucent and nearly invisible periosteal shadow. The distinguishing microscopic composition of loose myxomatous connective tissue merging into zones of fetal cartilage and chondral areas with an abundant hyaline matrix fringed by osseous tissue indicates its proliferative powers, yet identifies this sarcoma with the more benign tumors of the fibrocartilaginous group.

14. Hyndman, O. R.: Hereditary Deforming Chondrodysplasia: Report of a Case, *Arch. Surg.* **21**:12 (July) 1930.

15. Geschickter, C. F.: Osteogenic Sarcoma, *Arch. Surg.*, to be published.

CLINICAL FEATURES

The clinical features of primary chondrosarcoma reflect in part the primitive histogenesis of this neoplasm. The frequency with which Negroes are affected (approximately 15 per cent) is unusual among the osteogenic sarcomas as a group, and suggests a lower evolutionary form of osteogenesis for this tumor. The extremely malignant clinical course also implies a primitive tissue of origin. These clinical aspects of this neoplasm, the tendency for the tumor to be related to periarticular structures and the rapid clinical course with its usually fatal outcome may be singled out as fundamental characteristics of the growth.



Fig. 40 (P. N. 42358).—Roentgenogram and gross specimen of a primary chondromyxosarcoma. The patient was a white boy, aged 18, with an onset of symptoms one month previously of pain and tumor in the medial aspect of the lower end of the femur. The lesion was explored, and amputation done. The patient died nine months later. The roentgenogram, shows a translucent periosteal shadow above the internal condyle of the femur, with definite periosteal lipping above and radiating spicules (probably calcified) next to the bone. The gross specimen shows more definitely the actual size and location of the tumor mass, emphasizing the translucent character in the roentgenogram of most of the tumor substance.

These primarily malignant tumors occur in patients under 30, sarcoma of this form appearing as an initial lesion most frequently in patients from 14 to 21 years, in the postadolescent period (table 4 and

fig. 41). The youngest patient in this series affected with a primary chondrosarcoma was 6 years, the oldest 45.

The favorite sites for these lesions are about the knee and at the shoulder and pelvic girdles (fig. 42). The majority are about the knee in the lower end of the femur or upper end of the tibia, forty-six of seventy-nine of the neoplasms in this series being located at these points. In the lower end of the femur the line of insertion of the adductor magnus along the linea aspera and at the adductor tubercle on the medial condyle is the predominant focus. The point of origin of the lateral

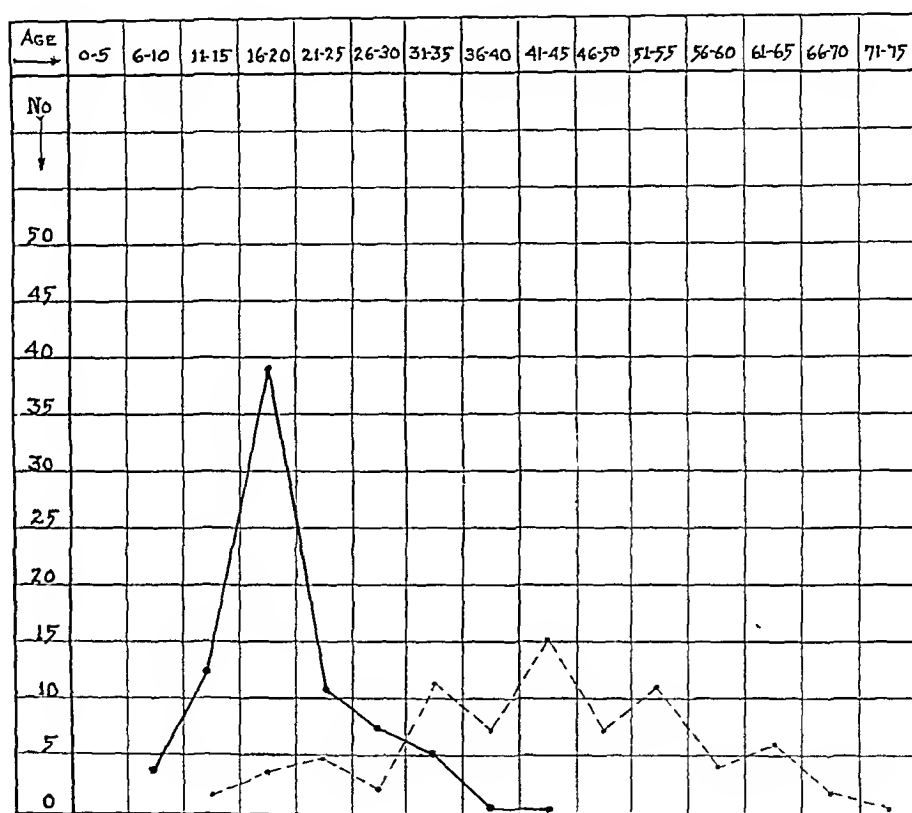


Fig. 41.—Chart showing age incidence among cases of primary chondromyxosarcoma. The solid line indicates the curve in seventy-nine cases of primary chondromyxosarcoma; the broken line, in seventy-five cases of secondary chondromyxosarcoma.

head of the gastrocnemius at the lateral femoral condyle is also occasionally involved. In the upper end of the tibia, the insertion of the quadriceps tendon at the tibial tuberosity is most frequently affected.

The distribution of these lesions shows a relationship to points of muscular attachment and to articular regions where cartilage formation persists throughout life. These sites of muscle attachment are, as has been seen, those of the long muscles exerting a maximal traction, such

TABLE 4.—Primary Chondromyxosarcoma

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
43820	W	M	34	Femur, lower	10	Pain; swelling	Translucent periosteal shadow	Amputation	Chondromyxosarcoma	Well 2 mo.
43610	W	F	18	Femur, lower	2	Pain; swelling	Translucent periosteal shadow	Irradiation	Living 1 yr.
42994	W	F	10	Femur, lower	7	Pain; swelling	Periosteal shadow, bone destruction	Curettement; amputation	Chondromyxosarcoma	Discharged well
42894	W	F	24	Humerus, right upper	2	Pain; swelling	Periosteal shadow, bone destruction	Biopsy; irradiation; amputation	Chondromyxosarcoma	Discharged well
42358	W	M	18	Femur, lower, medial	1	Tumor; pain	Translucent periosteal shadow; slight bone destruction beneath	Exploration; amputation	Chondromyxosarcoma*	Dead 9 mo. later†
42356	W	M	19	Femur, lower	2	Trauma	Translucent periosteal shadow; some radiating new bone	Exploration; amputation	Chondromyxosarcoma	Discharged well
42352	W	M	20	Tibia, lower	5	Trauma; pain; tumor	Translucent periosteal shadow at tuberosity	Amputation	Chondromyxosarcoma	Discharged well
42350	W	M	17	Femur, lower; internal condyle	5	Pain; tumor	Translucent periosteal shadow; slight bone destruction beneath	Amputation	Chondromyxosarcoma	Discharged well
42348	W	F	20	Tibia, upper	9	Pain; tumor	Translucent periosteal shadow; some radiating new bone	Exploration; excision; radium	Chondromyxosarcoma	Living 20 mo. after first operation
42346	W	F	13	Tibia, shaft	8	Trauma; tumor	Translucent periosteal shadow; some radiating new bone	Amputation	Chondromyxosarcoma	Well 3 yr.
42344	W	F	12	Femur, lower	2	Tumor	Translucent periosteal shadow; some radiating new bone	Erysipelas and prodigious toxins (Coley's)	Dead 7 mo. later
42312	W	M	18	Femur, upper	5	Tumor; pain	Translucent periosteal shadow	Exploration; amputation	Chondromyxosarcoma	Dead 11 mo. later
42228	W	M	23	Femur, upper, middle	2	Pain, 2 months; swelling, 1 week	Translucent periosteal mass; right angle new bone	Röntgen therapy	Living 6 mo. later
42178	W	M	15	Tibia, upper	5	Trauma; tumor	Translucent periosteal shadow at tuberosity	Irradiation	Living 2 mo. later
11812	W	F	11	Astragalus, left	1½	Pain; swelling	Periosteal roughening	Curetted; amputation advised but not done	Chondromyxosarcoma	Recurred
11562	W	M	16	Humerus, upper, left	..	Pain; tumor	Translucent periosteal shadow; radiating bone	Irradiation	Dead 6 mo. later
11502	W	M	44	Jaw, left, lower	4	Pain; teeth extracted; tumor	Area of bone destruction	Radium; excision	Chondromyxosarcoma	Living 6 mo.
11110	W	F	16	Fibula, right, upper	2½	Tumor	Destruction with periosteal roughening	Amputation	Chondromyxosarcoma	Dead 6 mo. later
11122	W	F	17	Tibia, upper	4½	Pain; swelling	Periosteal bone destruction and bone formation	Amputation	Chondromyxosarcoma	Well 10 mo. later
41092	W	M	6	Femur, upper	..	Tumor	Translucent periosteal shadow	Röntgen therapy	Chondromyxosarcoma	Well 10 mo. later

41016	W	F	16	Femur, lower	4	Pain; tumor; limp	Translucent periosteal shadow; bone destruction beneath	Amputation	Chondromyxosarcoma	Well 16 mo. later
41006	W	F	15	Femur, lower	..	Tumor	Translucent periosteal shadow; bone destruction beneath	Curetted; amputation later	Chondromyxosarcoma	Dead 6 mo. after amputation
40718	W	M	22	Tibia, head	..	Tumor	Amputation	Chondromyxosarcoma	Dead 8 mo. later; metastasis to chest and skull
40620	W	M	39	Humerus	1	Pain; stiffness	Translucent periosteal shadow; slight bone destruction beneath	Resection	Chondromyxosarcoma	Well 18 mo. later
40561	W	M	15	Tibia, upper	2	Pain; tumor	Amputation	Chondromyxosarcoma	Cachexia 11 mo. later
40494	W	M	32	Second rib and clavicle	6	Pain; tumor	Erysipelas and prodigious toxins (Coley's)	Dead 4 mo.
40484	W	M	12	Femur, lower	..	Pain	Translucent periosteal shadow; expansion and destruction	Roentgen therapy	Well 1 yr.
40350	W	F	16	Eleventh rib	3	Tumor	Expansion and destruction	Roentgen therapy and radium
39794	W	M	15	Femur, lower	1/2	Tumor; pain	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 11 mo. later
39724	W	M	14	Pubis	Periosteal new bone	Roentgen therapy	Well 29 mo. later
39180	W	M	12	Humerus, shaft	12	Tumor	Translucent periosteal shadow	Irradiation	Living 9 mo.
39140	W	M	9	Femur, lower	1	Pain; tumor	Exploration	Chondromyxosarcoma	Well 3 yr. later
38814	W	M	18	Femur, lower	6	Tumor	Periosteal translucent shadow	Excision	Chondromyxosarcoma	Recurring 6 mo. later
38620	W	F	15	Tibia, upper	6	Trauma; pain; tumor	Periosteal translucent shadow	Amputation	Chondromyxosarcoma	Well 4 mo. later
38566	W	M	..	Femur, shaft	..	Tumor; pain	Amputation	Chondromyxosarcoma	Dead 2 yr. later
38110	W	M	45	Jaw, lower	7	Pain; abscess	Bone destruction	Drainage and excision	Chondromyxosarcoma	Dead 2 yr. later
37930	W	M	18	Femur, lower	2	Trauma; pain	Translucent periosteal shadow	Irradiation; amputation	Chondromyxosarcoma	Dead 1 yr. later
37321	W	M	14	Tibia, upper	9	Pain; tumor	Translucent periosteal shadow	Roentgen therapy	Dead
36620	W	M	34	Humerus, shaft	..	Tumor	Translucent periosteal shadow	Irradiation; amputation	Dead 6 mo. later
36184	W	F	9	Tibia, upper	6	Trauma; pain; limp	Translucent periosteal shadow	Exploration; amputation; toxins	Chondromyxosarcoma	Dead 6 mo. later
35532	W	M	15	Femur, lower	2	Pain; tumor	Translucent periosteal shadow; radiating new bone	Irradiation; amputation	Chondromyxosarcoma	Dead 18 mo. later

* The term chondromyxosarcoma indicates a microscopic picture comprising: myxoma, fetal, adult and calcifying cartilage and occasional new bone formation.
† The results given show the duration calculated from the date of treatment. The duration of symptoms is from the subjective onset.

TABLE 4.—*Primary Chondromyxosarcoma—Continued*

Pathologic No.	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Röntgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
35010	W	M	23	Radius, shaft	3	Pain	Translucent periosteal shadow	Curettement
34084	W	M	26	Tibia, upper	..	Pain	Translucent periosteal shadow; bone destruction	Amputation; irradiation	Dead 1 yr. later
34056	W	M	17	Humerus, upper	27	Trauma; tumor	Translucent periosteal shadow	Roentgen therapy and serum	Dead 2 yr. later
33085	W	F	10	Humerus, upper	2	Trauma; pain; tumor	Translucent shadow of soft part	Irradiation	Dead 3 mo. later
32990	W	M	19	Tibia, upper	10	Pain; tumor	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 2 yr. later
32909	W	M	19	Femur, lower	3	Trauma; pain; tumor	Translucent shadow of soft part; bone destruction	Roentgen therapy; toxins; amputation	Chondromyxosarcoma	Well 10 yr. later
32348	W	F	16	Tibia, upper	3	Trauma; pain; tumor	Periosteal shadow; bone destruction	Irradiation; exploration	Chondromyxosarcoma	Dead 1 mo. later
32131	O	M	13	Femur, lower	3	Pain; swelling	Translucent shadow of soft part	Roentgen therapy	Lost
31940	C	F	25	Femur	8	Tumor	Translucent periosteal shadow; radiating new bone and bone destruction	Amputation	Chondromyxosarcoma
31523	W	M	14	Tibia, upper	4	Pain; tumor	Translucent periosteal shadow; radiating new bone	Excision; amputation	Chondromyxosarcoma	Dead 3 yr. later
30880	W	M	33	Iliac crest and pelvis	4	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Irradiation; toxins	...	Dead 1 yr. later
30175	C	F	33	Tibia, upper	17	Pain; tumor	Translucent periosteal shadow; bone destruction beneath at tuberosity	Resection; amputation	Chondromyxosarcoma	Lost
20103	C	M	22	Ulna, shaft	1	Pain; tumor	Translucent periosteal shadow; radiating new bone	Amputation	Well 6 yr. after

28501	W	M	19	Femur, lower	2	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Irradiation; amputation	Chondromyxosarcoma	Dead 2 mo. later
28700	..	F	25	Radius	6	Tumor	Exploration; eurette-ment; roentgen Amputation	Chondromyxosarcoma	Dead
28396	W	F	24	Tibia, upper	6	Tumor; pain	Periosteal translucent shadow	Amputation	Chondromyxosarcoma	Dead 5 yr. later
28239	W	M	18	Femur, lower	4	Pain; tumor	Amputation	Chondromyxosarcoma	Dead 2 yr. later (metastases to liver and intestines)
28057	W	M	16	Femur, lower	1	Trauma; tumor	Translucent periosteal shadow	Amputation; radium	Chondromyxosarcoma	Dead 3 mo. later (metastasis to bone)
27824	W	M	10	Tibia, upper	1	Pain; tumor	Translucent periosteal shadow	Excision	Chondromyxosarcoma	Dead 6 mo. later
27695	O	F	18	Femur, lower	4	Pain; tumor	Amputation; Irradiation	Chondromyxosarcoma	Dead 6 mo. later
27531	W	M	22	Femur, lower	2	Pain; tumor	Translucent periosteal shadow	Exploration; amputation	Died, second operation
23637	W	M	..	Femur, lower	Excision	Chondromyxosarcoma
21357	W	M	17	Femur, lower	1	Pain	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 13 mo. later
20160	W	M	14	Fibula, upper	2	Pain; tumor	Periosteal new bone; bone destruction	Incisions; eurette-ment	Chondromyxosarcoma	Dead 3 yr. later
19119	O	F	15	Femur, lower	3	Pain; swelling	Calcifying periosteal shadow	Amputation	Chondromyxosarcoma	Dead 7 mo. later
17584	O	F	14	Tibia, upper	6	Trauma; tumor	Amputation	Chondromyxosarcoma	Dead 3 yr. later
17525	W	M	20	Femur, lower	3	Trauma; tumor	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead
16347	W	F	25	Tibia, upper	8	Pain; tumor	Periosteal new bone; bone destruction	Amputation	Chondromyxosarcoma	Dead 15 mo. later
15538	W	M	21	Humerus	5	Pain; tumor	Amputation	Chondromyxosarcoma	Dead 13 mo. later
15557	W	M	21	Femur, lower	2	Pain; tumor	Periosteal new bone; bone destruction	Amputation	Chondromyxosarcoma	Dead 2 yr. later
11670	W	M	17	Tibia, upper	8	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Amputation	Chondromyxosarcoma	Dead 1 yr. later
8060	W	M	17	Sacrum, upper	12	Trauma; tumor; paraplegia	Exploration	Chondromyxosarcoma	Dead 1 yr. later
2331	W	M	17	Vertebra, lower lumbar	12	Trauma; pain	Exploration	Chondromyxosarcoma	Dead 1 yr. later
1890	W	F	22	Isthmum	48	Trauma; pain	Partial excision	Chondromyxosarcoma	Recurrence 3 mo. later, dead 1 yr.

as the rectus abdominus, the quadriceps femoris, the adductor magnus and the gastrocnemius. As in the exostoses, the points of origin for this type of tumor show an anatomic peculiarity in the periosteum. Here the normal fibrous layers of the periosteum are interrupted to allow osseous fusion with the end of a tendon, and at the point of fusion, pre-cartilaginous tissue, from which such structures as the adductor tubercle or the tuberosity of the tibia are formed, persists both beneath the periosteum and within the substance of the tendon.

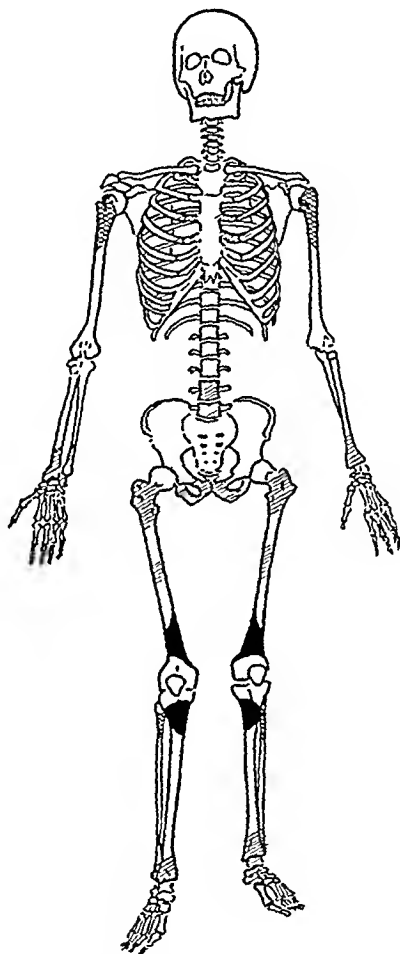


Fig. 42.—Incidence of primary chondromyxosarcomas according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites, and the diagonal lines, the occasional or rare locations.

The symptoms related by a patient suffering from this primary form of chondrosarcoma are confined to a period of about five months and begin with a complaint of pain, which may or may not follow a relatively mild form of trauma. The pain becomes rapidly more constant and severe and soon interferes with the function of the part. Since the region of the knee is usually involved, the stiffness of this joint, with the assumption of a position of partial flexion is a common condi-

tion. Weight-bearing in the affected leg soon becomes painful, and limping is followed by the use of crutches, full relief soon being impossible even when the painful region is put at complete rest.

Examination reveals swelling in the region of the flexed joint and a tumor with a rubbery consistency that is larger to palpation than the x-ray films would seem to indicate. Pathologic fracture is exceedingly rare because of the acute course and the periosteal nature of the lesion. Among the constitutional manifestations of primary chondrosarcomas, fever, leukocytosis and an enlargement of the regional lymph nodes are occasionally observed. The glandular enlargement is noted only in association with fever, and, to my knowledge, metastases to these glands have not been demonstrated by histologic examination, although such secondary growths in other forms of osteogenic sarcoma have been recorded in rare instances in this laboratory. These systemic reactions as well as a secondary anemia are late manifestations of the disease and should play no part in making the diagnosis.

ROENTGENOGRAPHIC FEATURES

Three important features are typical of the x-ray picture of primary chondrosarcoma. These are the faintly visible and fairly translucent shadow of the soft part next to the bone, the raising of the adjacent periosteum and the frequent absence of cortical or medullary involvement of the bone. The entire tumor is outside of the bone proper in early cases, and because its cartilaginous substance casts so little shadow on the film, this may well be considered the invisible tumor of the bone which is in danger of being overlooked or misdiagnosed by those unfamiliar with this early roentgenographic picture. When new bone or calcification of tumor origin is present, it is always sparse and has a tendency to take the form of finely radiating lines at right angles to the cortex (fig. 43). Unlike the "sun ray" or sclerosing type of osteogenic sarcoma, dense shaggy lines of periosteal new bone are lacking. This type of sarcoma also differs from the sclerosing form in that it is less likely to involve the marrow cavity, and when doing so late in the disease produces bone destruction in the medulla rather than areas of increased density as in the sclerosing form (Geschickter¹⁵).

This primary form of chondrosarcoma is to be distinguished from the benign osteochondromas in the roentgenogram, by its more faintly visible tumor shadow, by its more indefinite and infiltrating outward margin and also by the failure of the cortex beneath the tumor to form a base or pedicle for the growth as it does in exostoses. When such a chondromyxosarcoma arises as a secondary malignant change in a benign exostosis, this sarcomatous transformation in the benign tumor is evident in the roentgenogram by the blurring and blotting out of the

distinguishing lines differentiating cancellous from cortical bone in the base of the exostosis, and the whole tumor soon becomes a blurred and granulated mass (fig. 44). These secondary chondrosarcomas are discussed separately in more detail below.

The early stage of myositis ossificans may be mimicked (Lewis¹⁶) in appearance by the delicate lines of ossification in this form of chondrosarcoma, but in the sarcoma the outer border of the tumor never has the definite edge seen in myositis ossificans, and the laminated bony structure paralleling the shaft of the bone is absent. The favorite



Fig. 43 (P. N. 39114).—Roentgenographic appearance of the primary chondromyxosarcoma in which early signs of calcification and ossification are present in the tumor area next to the bone. Note the faintly visible periosteal shadow, the absence of cortical or medullary involvement in the bone and the location at the site of the adductor tubicle.

location of myositis ossificans in the adductor muscles of the thigh and the branchialis anticus of the elbow is not a common site of this form of osteogenic sarcoma, nor is there the same definite relationship to a trauma preceding the lesion by a period of from four to six weeks (fig. 9).

16. Lewis, D.: Myositis Ossificans, J. A. M. A. 80:1281 (May 5) 1923.

GROSS PATHOLOGY

Biopsy of these tumors reveals, beneath a raised and perforated periosteum, a pearly gray and shiny substance of varying consistency, some of it is well formed cartilage, other parts cystic and hemorrhagic. The various lobules that compose the tumor show a tendency to extend lengthwise up and down the bone and around it, rather than to invade the marrow cavity. However, in advanced cases, the cortex is broken through, and neoplastic tissue infiltrates the medulla of the bone. It is such advanced cases with involvement of the marrow cavity by cartilaginous tumor substance that are most common in the older literature, and for this reason there has been an erroneous conception that this type of tumor is of central rather than of periosteal origin (fig. 45).

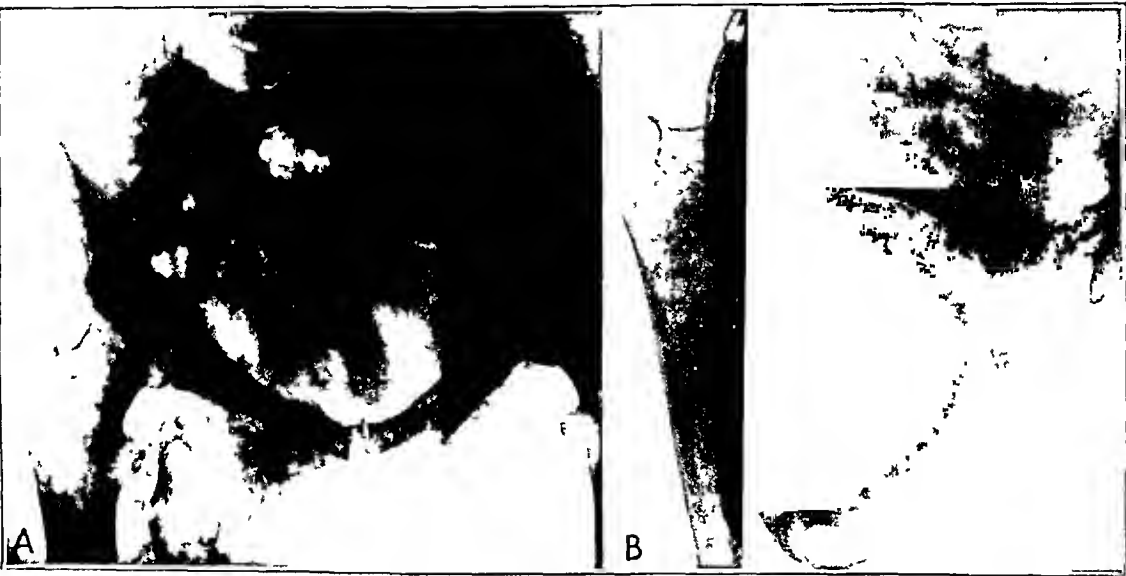


Fig. 44 (P. N. 32485).—Roentgenogram of a case of secondary chondromyxosarcoma arising in a benign osteochondroma. *A* shows the osteochondroma arising in the lower ramus of the pubic bone. *B* shows the same lesion three years later with definite malignant change. Note the granular character of the neoplasm, its immense size and the fracturing of the pubis and the ischium. The patient was a white woman, aged 30, who had known of the presence of the tumor for over three years. Deep roentgen therapy was administered, but the patient died of internal metastases five years after the treatment was begun.

Small pockets that exude a sanguineous synovial-like fluid are not rare in these growths. Such cystic areas containing what is a pseudo-joint fluid make the exploration of these neoplasms by one unfamiliar with their pathology an extremely dangerous procedure. Myxomatous tissue contained in the outpouring fluid is the mother substance of these tumors, and is even more readily transplanted than is the myxoma of the benign chondroma (fig. 46).

One of the striking features of the tumor growth is the metastasis or gradual extension into the large veins. H. J. B. Fry¹⁷ reported a case in which the tumor arising from the sacrum metastasized to the inferior vena cava and completely filled the right side of the heart with a soft cartilaginous mass. Phemister¹⁸ reported a similar case in which the cartilaginous growth filled the femoral vein by direct extension from a tumor arising in the femur.

In occasional gross specimens, the early lobules of the tumor may be seen sprouting from fibrous strands of a tendon such as the quadriceps



Fig. 45 (P. N. 19419).—Specimen of a primary chondrosarcoma in the lower end of the femur of a colored girl, aged 15. The periosteal tumor has invaded the marrow cavity, producing a dark cystic area shown in the right hand specimen. The clinical course was extremely brief, slightly over three months of symptoms and death within seven months after the primary amputation.

in the region where it envelopes the patella or the attachment of the adductor magnus at the line of insertion at the adductor tubercle. This relationship is particularly striking in some cases and may be verified

17. Fry, H. J. B., and Shattock, C. E.: Chondrosarcomatous Permeation of the Inferior Vena Cava and Right Side of the Heart, *Brit. J. Surg.* **14**:337, 1926.
18. Phemister, D. B.: Chondrosarcoma of Bone, *Surg. Gynec. Obst.* **50**:216 (Jan.) 1930.

microscopically by sections from properly chosen areas (fig. 47). Frequently, however, the tumor has extended sufficiently to obscure its mode of origin, and no definite conclusions can be drawn from the specimen.

MICROSCOPIC OBSERVATIONS

The analysis of microscopic sections of a series of cases of primary chondrosarcoma is essentially a study in miniature of the entire embryology of bone. Here the very earliest stages of cartilage formation from connective tissues can be found as well as the advanced calcifying



Fig. 46 (P. N. 41122).—Cysts in the chondromatous tissue of a primary chondrosarcoma occurring at the site of the tibial tuberosity. The patient was a white girl, aged 17, who complained of pain and swelling of four and a half months' duration. She has remained well ten months following a primary amputation.

forms. In addition, but less frequently, the phase of substitution bone which follows in the wake of calcified cartilage can be seen in the form of ossification proceeding from early connective tissue. At other times, although rarely, an intervening resorptive stage characterized by giant cell proliferation occurring before calcified cartilage is replaced by bone, can be found in the more slowly growing areas of these tumors. This rehearsal of the entire embryology of normal bone in distorted and abortive form by chondromyxosarcoma is explicable only on the basis

that the tissue of origin of this tumor represents the earliest type of undifferentiated connective tissue concerned with ossification. At this primitive stage, this tissue has the full potentialities of subsequent differentiation essential for all of the various structures of the future skeleton. Embryologically, such a tissue is best represented by the perichondrium which although primarily concerned with the proliferation of cartilage, subsequently differentiates into periosteum and develops the property of direct membranous bone formation. As previously explained, this perichondrium is closely allied or identified with the other types of precartilaginous connective tissue concerned with articular and periarticular functions.



Fig. 47 (P. N. 27695).—Photomicrograph showing the embryonic connective tissue and fetal cartilage cells of a primary chondromyxosarcoma arising from the ends of the tendon. The patient was a colored girl, aged 18, who complained of pain and tumor in the lower end of the femur of four months' duration. She died six months after a primary amputation followed by irradiation.

The fundamental basis of the pathologic process of primary chondromyxosarcoma is to be found under the microscope in nearly all of the sections taken from this type of tumor. Histologically, the growth arises from a dense condensation of embryo-like connective tissue. The cells of this tissue, which are either stellate or an elongated spindle shape, give origin to a syncytium (fig. 48) with an increasing amount of clear, hyaline-like ground substance, in which the connective tissue

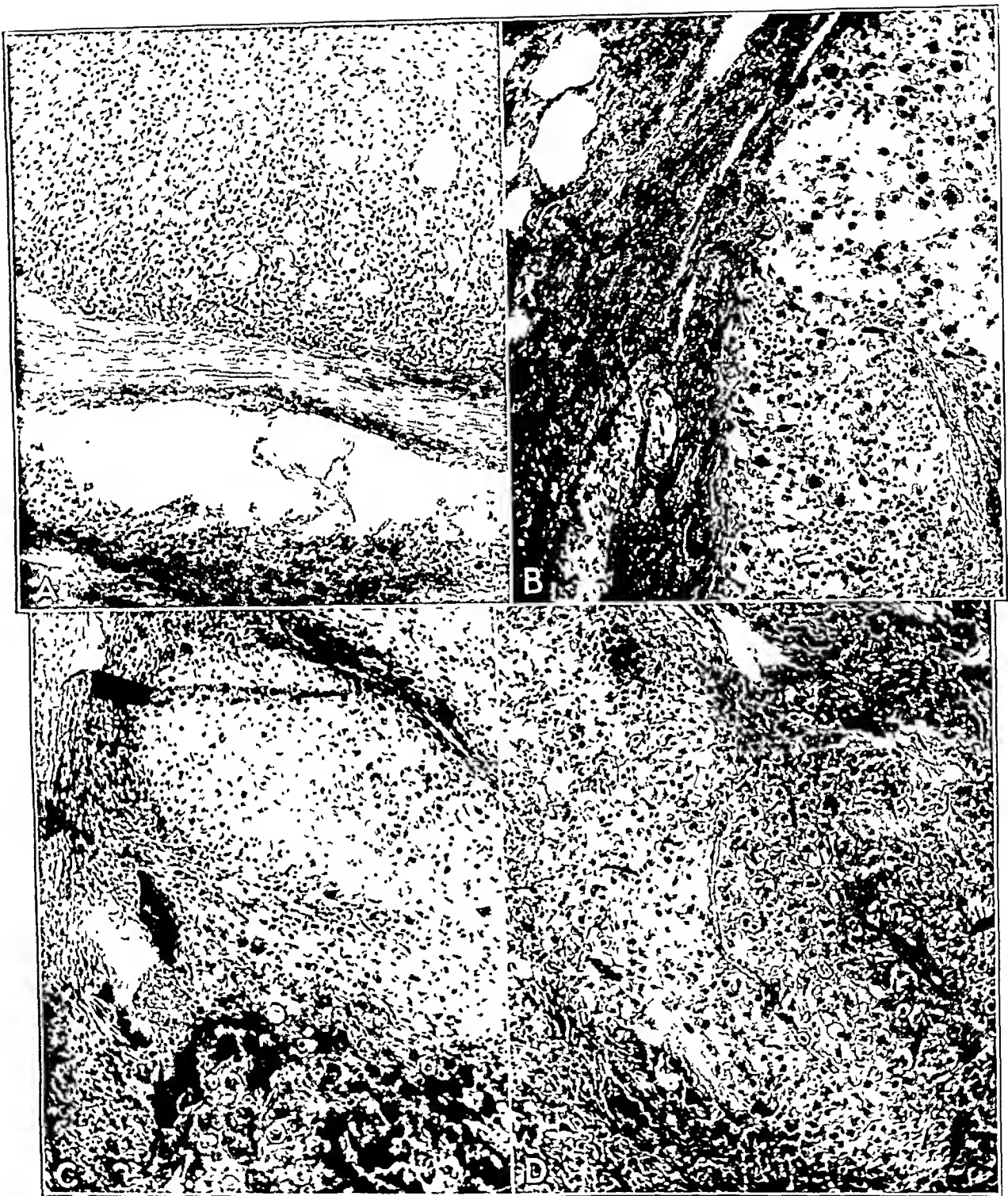


Fig. 48.—Studies showing the cycle of tissue differentiation in chondromyxosarcoma. *A* shows primitive connective tissue and fetal cartilage cells arising from a tendon adjoining the tumor. This is the myxomatous stage. *B* is from a metastatic lung nodule in a case of chondromyxosarcoma and shows the more adult cartilage cells developing in a myxomatous matrix. *C* shows the margin of the tumor in a case of chondromyxosarcoma in which the primitive precartilaginous connective tissue is giving rise to adult and calcifying cartilage. This is the cartilaginous stage. *D* is from the central portion of a chondromyxosarcoma and shows the primitive connective tissue in the tumor giving rise to direct bone formation of neoplastic origin.

cells after assuming a rounded form, become embedded. This syncytial tissue is typical myxoma, and the scattered rounded cells with small dense nuclei and clear, deeply acidophilic cytoplasm are fetal cartilage cells. Later these cells surround themselves with small lacunae, which gradually take a definite capsular form, abutting on the ground substance in a fashion that duplicates typical adult hyaline cartilage. This adult cartilage differs from that found at the normal epiphyseal line and in benign chondromas and osteochondromas in that the cells show less tendency to arrange themselves in definite columns and, in addition, contain nuclei that are larger, more vesicular and more frequently undergoing mitosis. Fibrous septums dividing the cartilage into lobules are also more frequent and far more cellular in these malignant growths, and calcification occurs more sporadically and irregularly.

This transition from fibrous tissue to cartilage with an intermediate syncytial or myxomatous stage (fig. 49) has been responsible for the connotation of chondromyxosarcoma given to this tumor. Contrary to the traditional views of Ribbert,¹⁹ Sternberg,²⁰ Kolodny,²¹ and others, the myxomatous substance in these lesions is not a product of cartilaginous degeneration but the predecessor of the later chondral forms which are derived from it, a view that is fully substantiated by the studies herein presented and with which Borst²² is in full accord. The fact that mucoid cysts and pockets of syrupy synovial-like fluid are to be found in association with these myxomatous areas is not a phenomenon of degeneration but concerns the embryologic rôle which this tissue plays in the formation of normal joint cavities.

Bone formation is not prominent in these primary chondrosarcomas. When found, the osseous tissue is usually next to the periosteum overlying the tumor and is either reactive bone, proceeding from normal periosteum, or ossification of tumor origin arising in the dense embryonal connective tissue strands dipping from the capsular margin into the tumor substance (fig. 50). The fact that the latter type of bone, thus produced, is neoplastic in origin and not reactive is substantiated by the finding of similar areas in metastatic nodules of the lung (figs. 51 and 52). This neoplastic ossification is always sparse in primary chondromyxosarcoma, but when it does occur it must be taken as an indication that the primitive perichondrium or precartilaginous connective tissue from which these growths arise is differentiating in two directions, one toward the proliferation of cartilage and the other a trans-

19. Ribbert, H.: *Geschwulstlehre für Aerzte und Studierende*, Bonn, F. Cohen, 1904.

20. Sternberg, K.: Personal interview with the author, July, 1929.

21. Kolodny, A.: *Bone Sarcoma: The Primary Malignant Tumors of Bone and the Giant Cell Tumor*, Surgical Publishing Company of Chicago, 1927.

22. Borst, M.: Personal interview with the author, July, 1929.

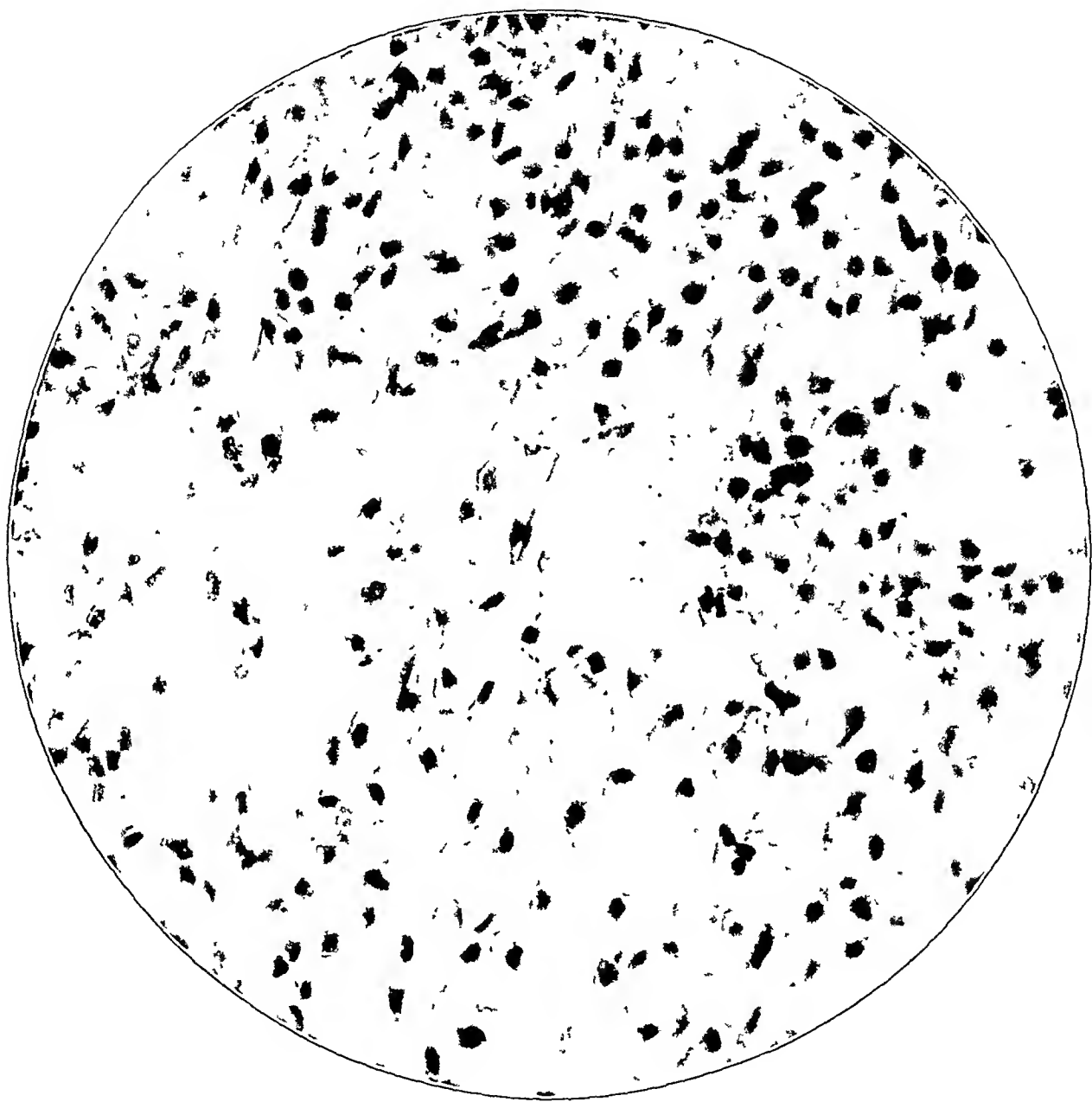


Fig. 49 (P. N. 27695).—High powered photomicrograph of the lesion depicted in figure 47. This illustrates clearly the differentiation of fetal cartilage cells from the spindle cells forming the so-called myxoma. In the lower part of the picture there is shown an early cartilage cell secreting a capsule about itself. The cartilaginous tissue in this case is clearly proliferated from the preceding myxomatous state, contrary to the traditional views that the myxomatous tissue is a degenerate product of cartilage.

formation toward adult periosteum with the production of direct membranous bone.

From a diagnostic standpoint, it is sometimes extremely difficult to be certain of the presence of chondromyxosarcoma under the microscope and to distinguish these lesions from the more cellular types of benign chondromyxoma. In a review of many sections, the cellular nature of the connective tissue strands, the presence of myxoma and fetal cartilage, the malignant nuclei of the cartilage cells and the occasional presence of cellular areas containing round cells midway between fetal cartilage



Fig. 50 (P. N. 32990).—Photomicrograph showing a primary chondromyxosarcoma. The patient was a white man, aged 19, with symptoms of pain and swelling of ten months' duration in the upper end of the tibia. The roentgenogram showed a translucent periosteal shadow with a few radiating spicules of new bone. Amputation was performed June, 1923. The patient died with metastasis to the lungs two and one-half years later, in 1926. The photomicrograph shows the periosteal border of the tumor. There is a proliferation of dense embryonic connective tissue with the formation of a hyaline matrix containing fetal and adult cartilage cells. The lower right hand corner shows calcifying adult cartilage. The small amount of new bone near the tumor capsule is proceeding from primitive connective tissue.

and chondroblasts in differentiation (fig. 53) have been found helpful in identifying chondromyxosarcoma.

HISTOGENESIS

From the standpoint of histogenesis, it is evident that this form of chondrosarcoma is related by location and by histology to primitive pre-cartilaginous tissue. Its occurrence at the sites where tendons attach directly to bone and participate in the formation of normal bony protuberances for the anchoring of such tendons shows that the developmental steps from connective tissues to cartilage to bone persist normally in these regions. Adequate evidence to substantiate such a



Fig. 51 (P. N. 31523).—Low powered photomicrograph of a metastatic nodule in the lungs of a patient dying of chondromyxosarcoma.

conclusion has been presented in tracing the histogenesis of the benign exostoses (see page 245, section marked Histogenesis).

The presence of this relatively undifferentiated fibrous tissue which retains such embryonic functions at the sites where chondromyxosarcomas arise does not necessarily represent fetal cell rests in the sense of Cohnheim.²³ The evidence educed here favors the view that the persistence of this tissue about periarticular points provides a normal

23. Cohnheim, J.: *Vorlesungen über Allgemeine Pathologie Ein Handbuch für Aerzte und Studierende*, Berlin, 1877-1880.

growth center which functions in maintaining tendon length in keeping with increased skeletal growth. This would account for the origin of these primary forms of ossifying chondrosarcoma during the age period of maximum skeletal growth, and would indicate that the normal

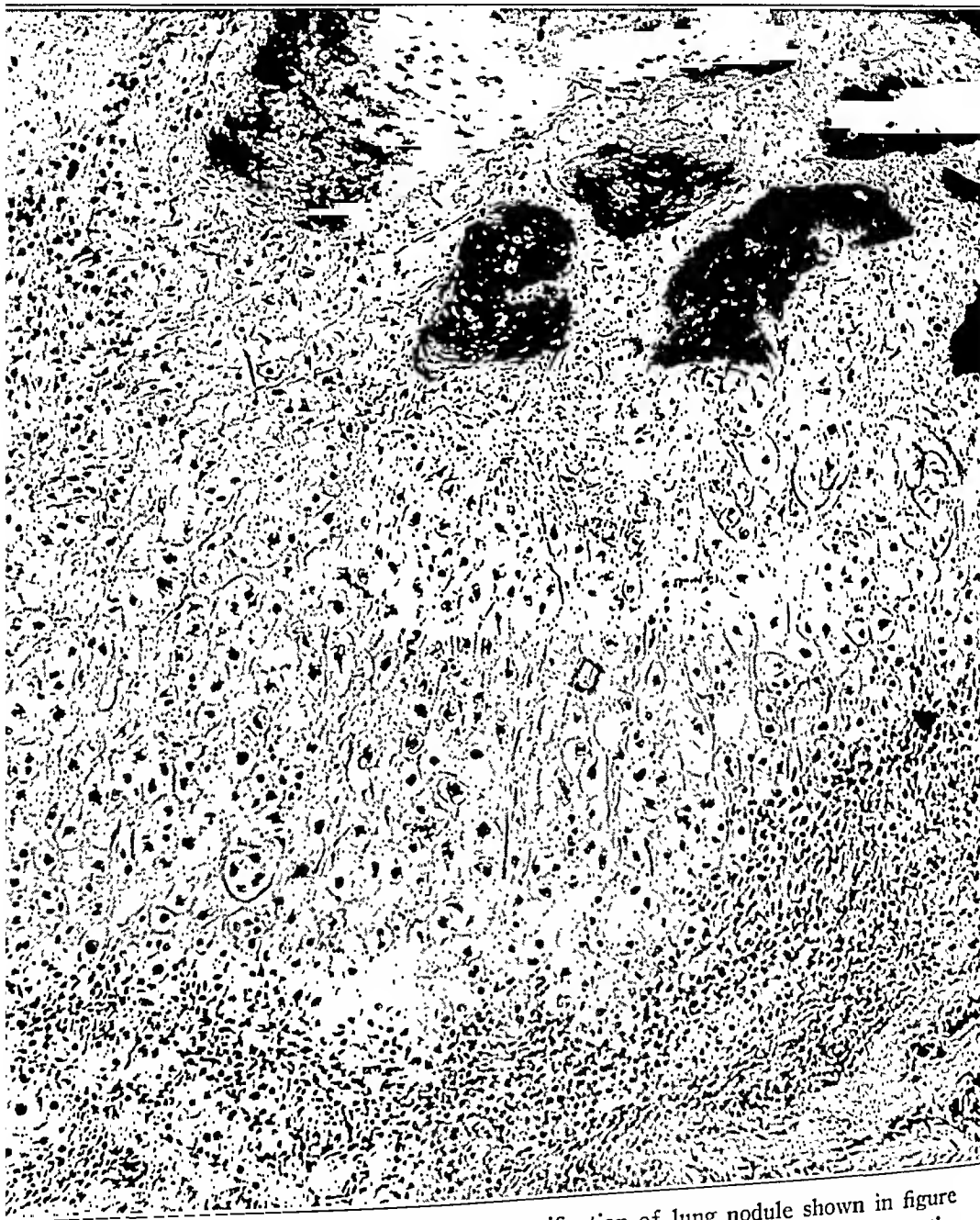


Fig. 52 (P. N. 31523).—Higher magnification of lung nodule shown in figure 51. The new bone depicted in the high power illustration shows clearly the power of bone formation residing in the primitive connective tissue found in this form of neoplasm.

cytologic transitions accompanying tendon growth form a fundamental basis for the origin of this tumor. This conclusion that both normal

growth impetus and a normal cycle of histogenic differentiation at a growth center is essential to the inception of this form of sarcoma of bone is substantiated by the study of the other types of osteogenic sarcoma which arise under similar circumstances.

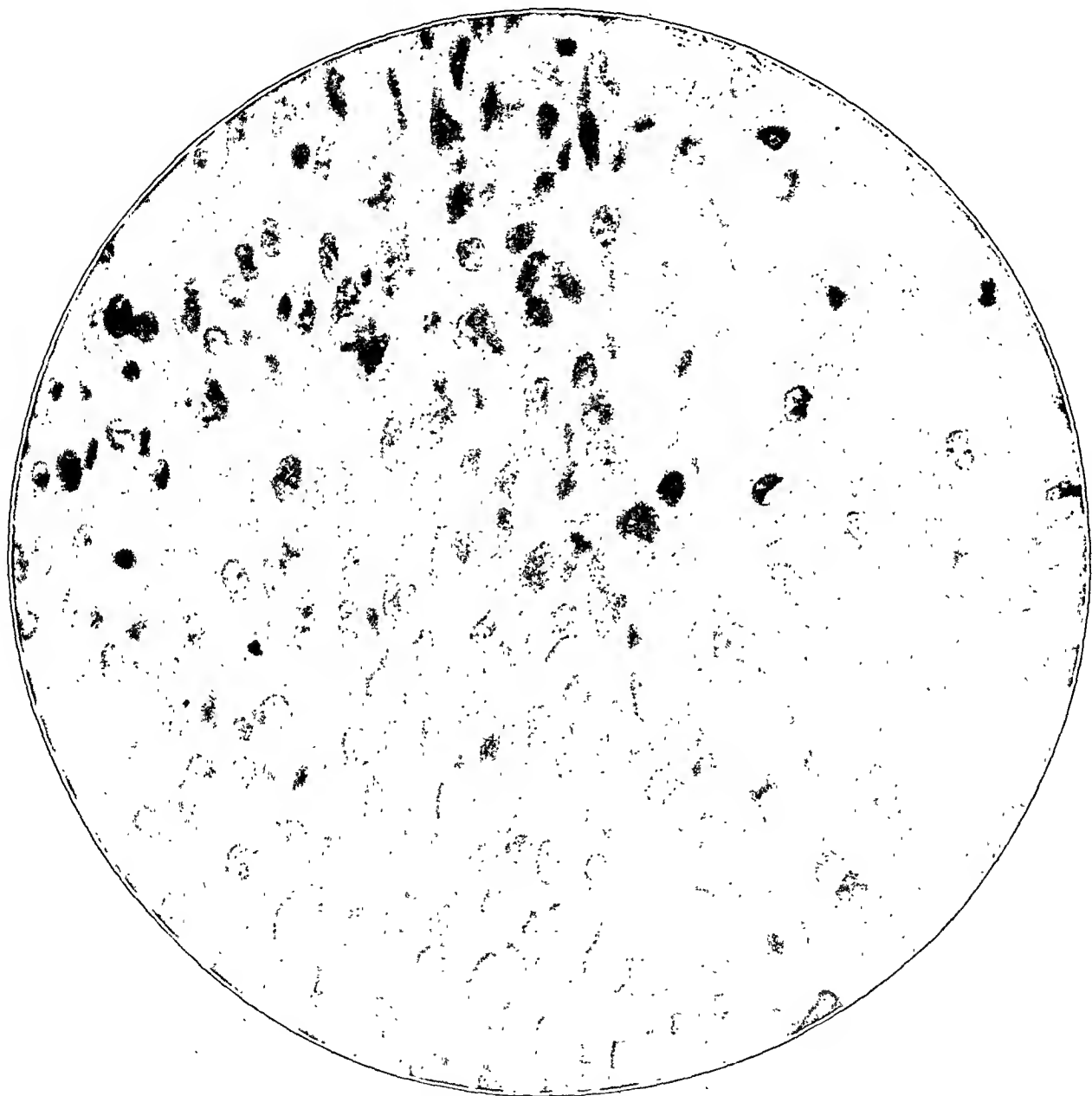


Fig. 53 (P. N. 20116).—Photomicrograph showing the cellular areas containing round cells midway between fetal and adult cartilage, characteristic of chondromyxosarcoma as distinguished from the benign chondroma.

The close similarity between the mode of origin of the benign exostoses and the primary chondromyxosarcomas raises the question concerning the factors which determine whether a given neoplasm will

pursue a benign or malignant course. For it is fairly certain that at their inception the developmental state of the mother tissues is practically the same for both benign osteochondromas and the malignant primary chondrosarcomas. Why, therefore, should the exostosis be such a slowly growing and benign affair and the chondromyxosarcoma with the same beginning, pursue such a rapid and malignant course?

The only explanation which comes to mind involves a matter of tissue balance, a subject on which there is little or no information. If one assumes that in exostoses the chondromyxomatous cap which represents the neoplastic portion of the tumor is in balance with the ossification which proceeds from the bone beneath and that the overgrowth is caused by an exaggerated periosteal gap, then it becomes feasible to assume that in primary chondrosarcoma no such balance exists, and the neoplastic chondromyxomatous tissue outstrips the adjacent ossification and attains its malignant properties.

On such a basis it is possible to explain the secondary origin of chondrosarcoma in previously benign osteochondromas. These secondary malignant growths arise when a previously existing balance is overthrown. This is usually in the adult when the adjacent bone has lost its power of ossification with increasing age, or in youth when trauma or some irritating agent acts to stimulate unduly, the growth propensities residing in the neoplastic tissue.

PROGNOSIS AND TREATMENT

Permanent cures, even when amputation is performed promptly without a previous exploration, are rare in this malignant form of primary chondrosarcoma. In a fatal case the patient usually lives approximately fourteen and one-half months after operation. Since the average duration of symptoms prior to operation is five and one-half months, a case of primary chondrosarcoma can be expected to run its entire clinical course within twenty months. Neither the age nor the location of the growth greatly influences the ultimate results, although apparently the prognosis is somewhat worse for children and when the lesion is in the upper end of the humerus and of the femur. Delay with prolongation of symptoms previous to operation accompanied by destruction of the medullary bone shown in the roentgenogram diminishes the prospect of a cure. Incomplete initial surgical treatment must be looked on unfavorably, but cures have been accomplished despite delay and recurrence after an initial operation.

If there is failure in the operative procedure, primary chondrosarcoma shows a marked tendency to recur locally as well as to metastasize. The total number of cures in the forty-two cases followed in this series for more than five years was two (table 5). In one case in

which amputation was performed, this procedure followed after radium treatments. In both of these cases microscopic verification of the diagnosis is available in the laboratory.

Deep roentgen therapy, either preceding the operation or given post-operatively, has no influence on the results as far as can be determined from this series of cases. When the patient has refused operation, deep roentgen therapy has apparently been helpful in alleviating pain, except in the more advanced stages of the disease. Its use, however, cannot be considered other than palliative in the dosages ordinarily administered. Radical resection and amputation, when used alone, are rarely successful in accomplishing a cure and should be used in conjunction with a radium pack. In lesions of the skeletal trunk radical excision or resection, followed by thermal cauterization and radium

TABLE 5.—*Results of Treatment in Cases of Primary Chondrosarcoma*

Total number of cases.....	77*
Lost	4
Total number of cases followed.....	73
Patients followed less than five years and reported well.....	18
Patients reported dead since 1925.....	13
Number of cases followed less than five years.....	31
Total number of cases followed for more than five years.....	42
Number of patients living over five years.....	2
Number of patients dead previous to 1925.....	40
Percentage of five year cures.....	5%

* Two recent cases have not been included in this table.

therapy is worthy of a trial. The dosage in such cases must be adequate (15,000 millicurie hours) and competently administered.

SECONDARY CHONDROSARCOMA

In all of the benign tumors of the fibrocartilaginous group, the persistence and functioning of connective tissue of the embryonic pre-cartilaginous type makes possible the origin of secondary chondrosarcoma which is superimposed on the original benign growth.

In many of such secondary lesions evidence of the preexistent growth is easily traced, but in others, in which an obscure and latent defect has been present for many years within the tuberosity of a long bone, urgent symptoms are not manifest until the condition has taken on frankly sarcomatous features.

Attention was first called to the latter type of tumor by Bloodgood²⁴ in 1906, under the term of pure myxoma of bone. While not con-

24. Bloodgood, J. C.: Bone Tumors, Myxoma, Central and Periosteal, *Ann. Surg.* 72:712 (Dec.) 1920.



Fig. 54 (P. N. 6773).—Secondary malignant change occurring in a benign exostosis. The cap of the lesion has been blotted out, and the base of the out-growth has been invaded by the destructive process of the chondrosarcoma. The patient was a white woman, aged 53, who had had a tender spot and a swelling on the shaft of the left humerus for over twenty years. She had noticed an increase in the lump for only nine months, with increased pain at this site. There was a history of syphilis dating back twenty-six years. This tumor was incised seven times within seven years, the final recurrence necessitating amputation at the shoulder joint. Three years after the amputation and ten years after the first operation, death occurred with metastases to the scalp and mediastinum. The microscopic structure of the tumor is shown in figure 66.

sidered primarily malignant, these lesions usually resulted in death from metastases after repeated recurrences over a period of years. To this clinical entity of Bloodgood, a secondarily malignant origin may now be ascribed on the basis of a restudy of all the cases thus classified by him in the Surgical Pathological Laboratory. These tumors occur most frequently in patients over 30 years of age and in the roentgenogram usually have the structure of a benign chondroma at their base within the bony tubercle but outwardly the translucent and indefinite shadow of a chondromyxosarcoma (fig. 54).

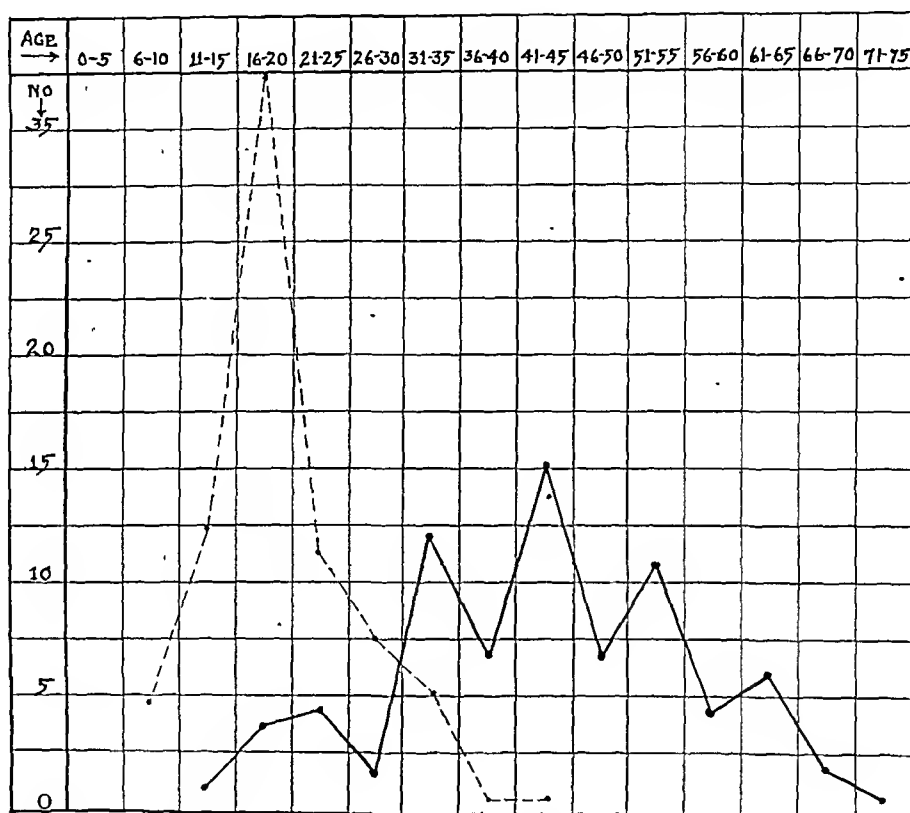


Fig. 55.—Age distribution in cases of secondary chondromyxosarcoma. The broken line shows the incidence in seventy-nine cases of primary chondromyxosarcoma; the solid line, in seventy-five cases of secondary chondromyxosarcoma.

CLINICAL FEATURES

Most of these tumors occur in persons between the ages of 35 and 55 (71 per cent), with the peak of incidence between the ages of 40 and 45. They may, however, occur before the age of 30 (fig. 55). The location of these neoplasms in the skeleton differs from the primary form of chondrosarcoma in that there is a greater tendency for them to occur at the upper end of the humerus, about the ribs and at the heel (fig. 56). The total duration of symptoms in these cases averages over six years in this series, varying from two to twenty-five years.

TABLE 6.—*Secondary Chondromyxosarcoma*

Pathologic No.	Race	Sex	Age	Location	Duration, Yrs.	Symptoms	Primary Condition	Röntgenographic Appearance	Treatment	Microscopic Changes	Result of Treatment
43831	C	F	22	Fibula, upper	4	Tumor; pain	Osteochondroma	Granular periosteal new bone	Resection; irradiation	Chondromyxosarcoma	Discharged well
43255	W	M	35	Femur, greater trochanter	8	Tumor	Chondroma	Trochanter destroyed; medulla rarefied	Excision	Chondromyxosarcoma
43252	W	M	50	Lower end of femur	Chondroma	Amputation	Chondromyxosarcoma
42388	W	M	50	Humerus, upper	2	Pain; tumor	Chondromatosis	Bone expansion; new bone formation	Resection	Chondromyxosarcoma	Dead after operation
42390	W	M	50	Pubis, left	25	Trauma; tumor; pain; edema	Osteochondroma	Granular periosteal new bone	Irradiation	Dying
42388	W	M	31	Os calcis; fibula, lower	2	Pain; tumor	Osteochondromas at old fracture site	Large translucent mass about achilles' tendon	Exploration; amputation	Chondromyxosarcoma	Well 5 yr.
42386*	W	M	40	Femur, lower	22	Trauma; pain; tumor	Exostoses; chondromatosis in and about knee joint	Multiple exostoses; joint mice; translucent periosteal shadow	Curettement; amputation	Chondromyxosarcoma	Well 1 yr. later
42382	W	M	47	Rib, third anterior	7	Tumor	Chondroma	Expanded osteochondral junction; translucent periosteal shadow	Resection (3 times)	Chondromyxosarcoma	Three recurrences; dead after 6 yr.
42354	W	M	19	Tibia, upper	..	Tumor, congenital (?); recent pain	Osteochondroma	Pedicle exostoses undergoing destruction and proliferation	Exploration (3 times); amputation	Chondromyxosarcoma	Living 21 mo.
42280	W	M	41	Ischium	..	Tumor; pain	Osteochondroma	Secondary bone destruction in exostosis	Curettement	Chondromyxosarcoma	Recurrence
41528	W	M	35	Humerus, greater tuberosity	5	Tumor	Chondroma	Tuberosity destroyed; acromion rarefied	Amputation	Chondromyxosarcoma	Well 1 yr. later
41103	Excision	Chondromyxosarcoma	Recurrence
10778	W	M	30	Tibia, upper	2	Pain; tumor; pathologic fracture	Osteochondroma	Translucent periosteal shadow; bone destruction beneath	Curettement (2 times); irradiation; radium and toxins	Chondromyxosarcoma	Recurrence
40612	W	M	15	Metatarsal base, second	2	Tumor; trauma	Chondroma	Central destruction; periosteal roughening	Excision	Chondromyxosarcoma	Dead 1 yr. later
10606	W	M	21	Femur, lower, left; toes right foot	2	Multiple tumors; elephantiasis	Chondroma (?)	Diffuse translucent periosteal shadow; rarefaction of phalanges	Amputation, left leg and right foot	Chondromyxosarcoma	Metastases
10150	W	M	30	Popliteal space	15	Trauma; tumor; pain	Chondromatosis	Translucent shadow of soft spot	Excision	Chondromyxosarcoma	Well 2 mo.
10273	W	F	54	Femur, lower	..	Tumor	Osteochondroma (?)	Exploration	Chondromyxosarcoma	Lost

40151	W	F	62	Scapula, left	1/2	Tumor; pain	Irradiation; colloidal lead; amputation	Chondromyxosarcoma	Well 2 yr. after operation
39952	C	M	18	Femur, lower, left	3	Trauma; tumor	Osteochondroma	Rounded exostosis; translucent shadow of soft part; new bone	Amputation	Chondromyxosarcoma	Well 8 mo.
38666	W	F	37	Femur, lower, left	1	Trauma; tumor	Chondroma	Translucent periosteal shadow; new bone formation	Excision; amputation	Chondromyxosarcoma	Recurrence; living 2 yr.
37868	W	M	29	Femur, upper	8	Tumor	Osteochondroma	Granular periosteal new bone	None	Dead 2 mo. later
37834	W	M	..	Skull, occipital	..	Tumor	Chondroma	Excision	Chondromyxosarcoma	Discharged well
37218	..	M	35	Upper end of humerus	..	Trauma; tumor	Periosteal bone formation	Partial resection	Chondromyxosarcoma	Recurrence; dead 4 yr. after operation
37114	W	F	30	Ribs, right	1	Tumor; pain	Chondroma	Resection	Chondromyxosarcoma	Discharged well
37022	W	F	40	Humerus, upper right	4	Trauma; tumor; pain	Osteochondroma	Translucent periosteal shadow	Resection	Chondromyxosarcoma	Well 10 mo. later
35914	W	M	42	Femur, trochanter	20	Tumor; pain	Osteochondroma	Bone destruction; translucent periosteal shadow	Curettement	Chondromyxosarcoma	Recurrence
35414	W	M	19	Femur, lower	9	Pain; swelling	Osteochondroma	Translucent periosteal shadow with bone destruction	Amputation advised	Well 6 yr. later
34618	W	M	49	Femur, lower, left	2	Pain; pathologic fracture	Chondroma	Translucent periosteal shadow; rarefied bone beneath	Curettement; irradiation	Chondromyxosarcoma	Well 6 yr.
34560	W	M	20	Femur, lower shaft	8	Pain; swelling; tumor	Exostosis and shadow of soft part	Excision; amputation; irradiation	Chondromyxosarcoma
34522	W	F	41	Femur, lower, left	28	Trauma; stiffness; pain	Chondroma	Translucent periosteal shadow; bone destruction beneath	Exploration; amputation	Chondromyxosarcoma	Metastases to frontal bone 4 yr. later
34360	W	F	30	Fibula, lower	1	Tumor	Chondroma	Cystic area of bone destruction	Curettement	Chondromyxosarcoma	Lost
34320	W	M	49	Ilium, right	3	Pain; stiffness	Chondroma	New bone; bone destruction	Excision; radium	Chondromyxosarcoma	Dead 3 yr. later
34166	W	M	51	Pelvis, acetabulum	1	Trauma; pain; tumor	Osteochondroma	Rarefaction; expansion of acetabular margin	No operation	Chondromyxosarcoma	Dead 4 1/2 yr. later; autopsy
33423	W	M	49	Femur, greater trochanter, right	2	Trauma; pain	Chondroma	Translucent periosteal shadow; bone destruction beneath	Curettement (13 times); amputation	Chondromyxosarcoma	Dead 4 yr. later
33052	W	M	25	Tibia, upper shaft	1 1/2	Trauma; pain; pathologic fracture	Chondroma	Translucent shadow of soft part	Exploration; resection; irradiation	Chondromyxosarcoma	Well 7 yr. later
33008	W	F	75	Humerus, upper right	4	Pain; tumor	Chondroma	Translucent periosteal shadow; bone destruction beneath	No operation	Chondromyxosarcoma	Dead 2 yr. later; autopsy
32608	W	M	69	Tibia, upper, left	1	Pain; tumor	Chondroma	Translucent periosteal shadow at tuberosity; diffuse bone destruction of upper shaft	Many eutectings; amputation	Chondromyxosarcoma	Well 3 yr.
32485	W	F	30	Iscium, right	3	Tumor; pathologic fracture	Osteochondroma	Granular periosteal new bone	Irradiation	Dead 5 yr. later
32317	W	M	25	Femur, mid-right	1 1/2	Trauma; swelling; pain; tumor	Large enlarging periosteal tumor (exostosis)	Exploration; amputation	Chondromyxosarcoma	Suicide, 1929

TABLE 6.—Secondary Chondromyxosarcoma—Continued

Pathologic No.	Race	Sex	Age	Location	Duration, Yrs.	Symptoms	Primary Condition	Röntgenographic Appearance	Treatment	Microscopic Changes	Result of Treatment
30344	W	F	39	Pubis, right	3	Pain; tumor	Osteochondroma	Bone destruction; translucent periosteal shadow	Curettement	Chondromyxosarcoma	Recurrence
30249	W	M	30	Femur, lower	3	Tumor	Metaphysical widening; periosteal tumor	Exploration	Chondromyxosarcoma	Dead 1 yr. 3 mo. later
30246	W	M	30	Femur, lower	3	Tumor	Osteochondroma (?)	Exploration	Chondromyxosarcoma	Dead 11 mo. later
30186	W	M	40	Femur, lower	Rarefaction and cortical expansion of shaft	Amputation	Well 5 yr., lost
29819	W	M	18	Astragalus	4	Pain; tumor	Chondroma	Bone destruction; radiating new bone	Exploration; amputation	Chondromyxosarcoma	Well 5 yr. after amputation
29616	W	M	64	Tibia; fibula; pelvis	½	Trauma; pain	Ossifying periostitis; Paget's disease (?)	Ossifying periostitis; translucent mass in popliteal space	Irradiation; amputation	Dead 7 mo. later
29613	W	F	54	Femur, lower	½	Pain; tumor	Osteochondroma	Translucent periosteal shadow over exostosis	Excision (?)	Lost
29559	W	F	53	Humerus, upper	1	Tumor; pain	Osteochondroma	Granular periosteal new bone	Excision; irradiation	Chondromyxosarcoma	Dead 1 mo. later
29467	W	M	29	Humerus, mid-shaft	..	Tumor and tenderness	Osteochondroma	Translucent periosteal shadow; bone destruction	Resection; roentgen therapy	Well 7 yr. 5 mo.
29382	W	M	42	Ilium, acetabulum	½	Trauma; pain	Osteochondroma	Periosteal roughening; bone destruction beneath shadow	Curettement; radium	Chondromyxosarcoma	Dead 9 mo. later
28639	W	F	55	Tibia, upper	¼	Pain; tumor	Chondroma	Translucent periosteal shadow	Amputation	Chondromyxosarcoma	Dead 2 yr. later
28338	W	M	45	Humerus, upper	20	Pain	Tremendous bone destruction; multiple periostitis	Chondromyxosarcoma	Dead; metastasis to bone and lungs
28413	C	F	17	Ninth rib	4	Pain; tumor	Chondroma	Resection (twice)	Chondromyxosarcoma	Well 9 yr. after second operation
28398	W	F	8	Tibia, upper	30	Osteochondroma	Translucent periosteal shadow; bone destruction; multiple exostoses	Curettement; radium	Chondromyxosarcoma	Well 11 yr.
28246	W	F	41	Vertebra, fourth lumbar	41	Congenital multiple tumors	Multiple chondromas, hereditary	Translucent periosteal shadow; bone destruction; multiple exostoses	Exploration	Dead 2 yr. later
27791	W	M	34	Scapula; spine	7	Trauma; tumor	Chondroma	Rarefied expanded area; bone destruction beneath	Curettement	Chondromyxosarcoma	Lost
27286	W	M	14	Femur, shaft	1/12	Trauma; tumor	Amputation	Chondromyxosarcoma	Well 20 yr. later
27222	W	F	33	Rib at sternum	1	Tumor	Chondroma	Curettement (3 times); radium	Chondromyxosarcoma	Recurrence, lost
26721	W	M	13	Humerus, upper	3	Pain; tumor	Chondroma	Translucent periosteal shadow; bone destruction beneath	Irradiation; resection; amputation	Chondromyxosarcoma	Dead 20 mo. later
25305	W	F	70	Femur, lower	½	Pain; tumor	Osteochondroma	Granular periosteal new bone	Amputation	Chondromyxosarcoma	Dead 1 yr. later
24984	W	F	12	Femur, lower	21	Tumor	Osteochondroma; chondrodermatoma	Bone expansion; granular periosteal new bone	Dead 1 yr. later

22929	W	M	40	Astragalus	30	Trauma; tumor; pain	Osteochondroma	Translucent periosteal shadow with new bone	Resection; amputation	Chondromyxosarcoma	Dead 3 yr. later; metastasis to other bones
19545	W	M	43	Os calcis	1	Pain; tumor	Osteochondroma	Translucent periosteal shadow	Curettement; amputation	Chondromyxosarcoma	Recurrence; living 3 yr.
19133	C	M	37	Humerus, upper	2	Pain; tumor	Chondroma	Bone expansion; translucent periosteal shadow	Amputation (2 times)	Chondromyxosarcoma	Dead 10 mo. later
18750	W	M	34	Pubis	1	Tumor	Osteochondroma	Granular periosteal new bone	Resection	Chondromyxosarcoma	Died at operation
15977	W	F	60	Tibia, shaft	3	Tumor; pain	Paget's disease	Osteitis deformans; translucent periosteal shadow; bone destruction	Amputation	Chondromyxosarcoma	Dead 7 mo. later
15395	W	M	49	Sternum, upper	3	Tumor	Partial excision	Chondromyxosarcoma	Well 9 yr. later
16327	W	M	62	Humerus, upper	3	Trauma; pain; tumor; previous abscess	Chondroma	Translucent periosteal shadow; new bone; bone destruction	Amputation	Chondromyxosarcoma	Lost
13511	W	M	24	Jaw, lower, left	2	Tumor	Osteochondroma	Periosteal new bone; bone destruction	Excision (2 times); resection; radium	Chondromyxosarcoma	Recurrence; living 7 yr.
12943	W	M	48	Femur, lower	27	Pain; tumor; pathologic fracture	Osteochondroma	Curettement (2 times); amputation	Chondromyxosarcoma	Dead 3 yr. later
12221	C	M	52	Humerus, lower	14	Pain; tumor	Osteochondroma	Excision	Chondromyxosarcoma	Lost
10150	W	F	35	Femur, lower, left	6	Tumor	Osteochondroma	Granular periosteal new bone; rounded exostosis	Excision	Chondromyxosarcoma	Dead 4 yr. later
10000½	W	M	52	Pelvis	1 & ½	Tumor	Exploration	Chondromyxosarcoma	Dead 1 yr. later
9339	W	M	42	Ribs	14	Multiple tumors	Chondromas	Excision	Chondromyxosarcoma	Dead 10 mo. later
8475	C	M	60	Humerus, upper	1	Pain; tumor	Chondroma	Curettement	Chondromyxosarcoma	Dead 4 yr. later
8111	W	M	56	Os calcis, right	25	Pain	Excision; amputation	Chondromyxosarcoma	Recurrence; dead (?)
6773	W	F	60	Humerus, upper	10	Trauma; pain; tumor	Osteochondroma	Exostosis undergoing destruction	Excision (4 times); amputation	Chondromyxosarcoma	Dead 3 yr. after last operation
1972	W	M	51	Femur, lower	3	Stiffness; tumor	Chondroma	Translucent periosteal shadow; bone destruction	Amputation	Chondromyxosarcoma	Dead 3 mo. later
908	W	M	70	Humerus	1 & ½	Trauma; pathologic fracture	Periosteal shadow	Amputation	Chondromyxosarcoma	Dead 13 yr. later from other causes
715	W	M	67	Jaw, lower	3	Pain; tumor; extraction of teeth	Osteochondroma	Bone absorption; pathologic fracture	Excision	Chondromyxosarcoma	Well 3 yr., lost
532	W	M	50	Ribs	..	Four repeated fractures of ribs	Excision	Chondromyxosarcoma	Local recurrence; dead 3 wk. after discharge

When this sarcoma develops secondarily in a benign cartilaginous growth, the history of the earliest phases of the disease can usually be elicited by careful questioning. The typical story given by such patients may begin with an injury many years before, the effects of which have subsided without apparent trace, or which remain in the form of a persisting lump of stationary size. There may be a history of rheumatic pains for many years or the consciousness that the affected limb has

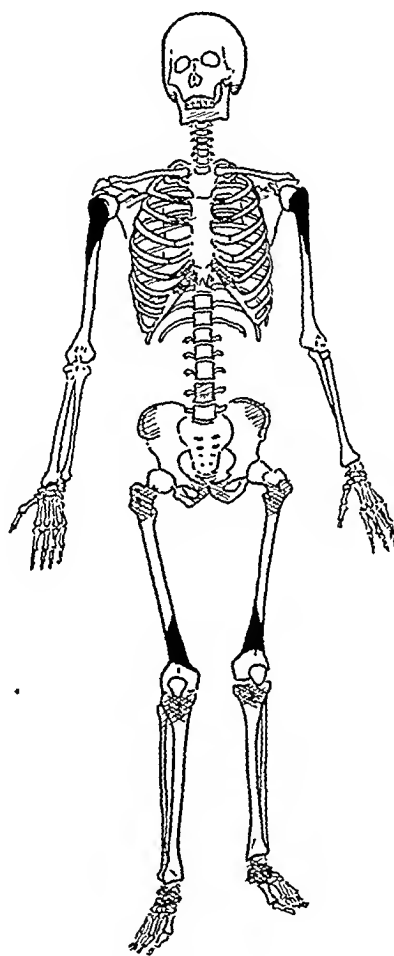


Fig. 56.—Incidence of secondary chondromyxosarcoma according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites; the diagonal lines, the occasional or rare sites.

always been crooked or shorter than the corresponding normal member. After an interval of years, and without obvious provocation, pain, swelling or pressure phenomena will cause an exacerbation of the previous trouble and lead the patient to consult his physician. In one instance a farmer had been kicked in the pubic region by a horse twenty-five years before, and a small stationary tumor had developed. In the two months preceding examination, a rapidly growing pelvic mass (arising

from the pubic bone near the symphysis) had caused pain and edema in the left leg because of blockage of the venous return. A similar case of sarcoma in a woman 50 years of age occurred twenty years after rheumatic pains in the upper part of the arm near the deltoid muscle at the site of an old exostosis.

The actual onset of malignancy in such neoplasms is difficult to establish. In some instances, the first lesion is obviously congenital. Judging from the primary form of this sarcoma and the subsequent rapid clinical course, the malignant change in these secondary tumors does not precede the onset of the acute symptoms by many months. However, the history of the case is often sufficiently vague so that the clinician must be on his guard against making a diagnosis of a benign osteochondroma on the mere circumstances of the long duration of the

TABLE 7.—*Clinical Features of Primary and Secondary Chondrosarcoma*

	Primary	Secondary
Origin.....	Junction of tendon to bone	Previous benign skeletal tumors
Sex.....	Males, 2:1	Males, 2:1
Race.....	Blacks, 15%	Blacks, 6%
Most frequent ages.....	14 to 21 years	30 to 50 years
Favorite sites.....	About knee; upper end of humerus	Shoulder and pelvic girdle; knee and heel
Duration of symptoms.....	3 to 5 months	2 to 25 years
Usual symptoms.....	Pain; tumor; tenderness	Pain; tumor; tenderness
Trauma.....	22%	22%
Pathologic fracture.....	None	6%
Constitutional manifestations.....	Occasional fever; leukocytosis; enlargement of regional lymph nodes; secondary anemia	Systemic reactions rare; secondary anemia

symptoms given. The degree of pain and the rapidity of the tumor growth are more trustworthy guides from the standpoint of diagnosis, but here again it must be borne in mind that benign exostoses which have been subjected to insufficient operation may, in rare instances, show similar features on recurrence, although no malignant change has taken place. In such instances, the x-ray picture and the biopsy constitute the most conclusive evidence. Nevertheless, it is a good clinical rule always to suspect a secondary chondromyxosarcoma when a history of indefinite rheumatic pains for a period of from five to ten years is obtained from an adult with a lesion in the region of a condyle or tuberosity of a long bone followed recently (in the space of a few weeks) by a change in the character and intensity of the symptoms.

This is well illustrated by a recent case of a physician, 31 years of age, who had a lesion in the internal malleolus of the left tibia (fig. 57). From a roentgenographic standpoint, this tumor was misdiagnosed a benign giant cell tumor. The location in an epiphysis, the central area

of destruction and the age of the patient were consistent with such a diagnosis. However, the patient gave a history of injury and continued weakness with occasional rheumatic pains in the left ankle dating back nineteen years. The acute symptoms of stiffness and soreness had been present only six weeks. This history suggested a secondary chondromyxomatous lesion, which was verified at operation.

Trauma incident to the malignant change occasionally occurs in this group of tumors, but often the injury relates to the original benign

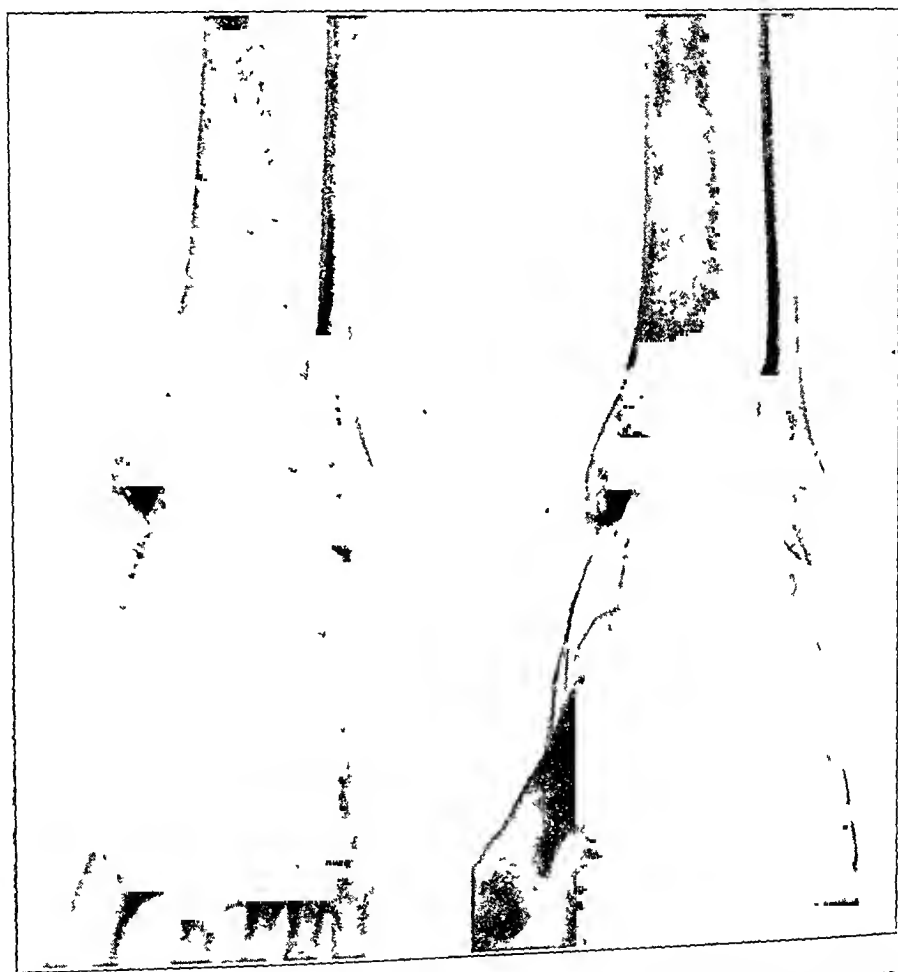


Fig. 57 (P. N. 43022).—Roentgenogram of a small chondromyxosarcoma embedded within the malleolus of the tibia. The patient gave a history of injury and continued weakness in the left ankle at this point dating back nineteen years. The acute symptoms of stiffness and soreness had been present six weeks. The lesion was excised and cauterization with 50 per cent zinc chloride was used. The patient has continued well for seven months.

growth and is to be associated with the incidence of trauma found in exostoses and kindred lesions (from 30 to 40 per cent). Pathologic fracture occurs in 6 per cent of secondary chondrosarcomas, and in these cases the line of fracture often extends through the protruding tumor mass rather than through the body of the bone (fig. 58).



Fig. 58 (P. N. 32317).—Secondary chondromyxosarcoma arising at the site of an old exostosis in a white man, aged 25. The malignant change occurred eighteen months previously, as far as can be determined, following a severe blow to the right thigh by an automobile crank. The tumor was explored, and the sections pronounced chondrosarcoma. Amputation was advised, but refused. The patient carried the tumor for four years longer at which time there was a pathologic fracture, and the tumor had reached such size that the patient consented to amputation, the specimen weighing 72 pounds (32.7 Kg.). The patient remained well two years after operation, despite a transient hemiplegia which occurred postoperatively. Six years after the first examination, however, his health began to fail, he became despondent and committed suicide by multiple stab wounds to the abdomen. Autopsy was not obtained. The roentgenogram shows the original base of the exostosis and the splintering of bone and spotty calcification typical of secondary chondromyxosarcoma.

ROENTGENOGRAPHIC FEATURES

The most easily recognized secondary chondrosarcoma is that in which distinct evidence of the nature of the primary lesion persists in the x-ray film and in which the superimposed malignant change is visible as a fuzzy infiltrating periosteal shadow. When a previous



Fig. 59 (P. N. 23284).—Roentgenogram of a secondary chondromyxosarcoma in a white woman, aged 44, who had had pain and swelling of increased severity in this region for two years, and who died one year after the picture was taken. The patient refused any form of treatment. The metaphyseal widening in this femur is indicative of a preexisting osteochondroma in this region.

osteochondroma is implicated, the evidence of this original lesion is usually visible in the form of a widened metaphyseal region in the

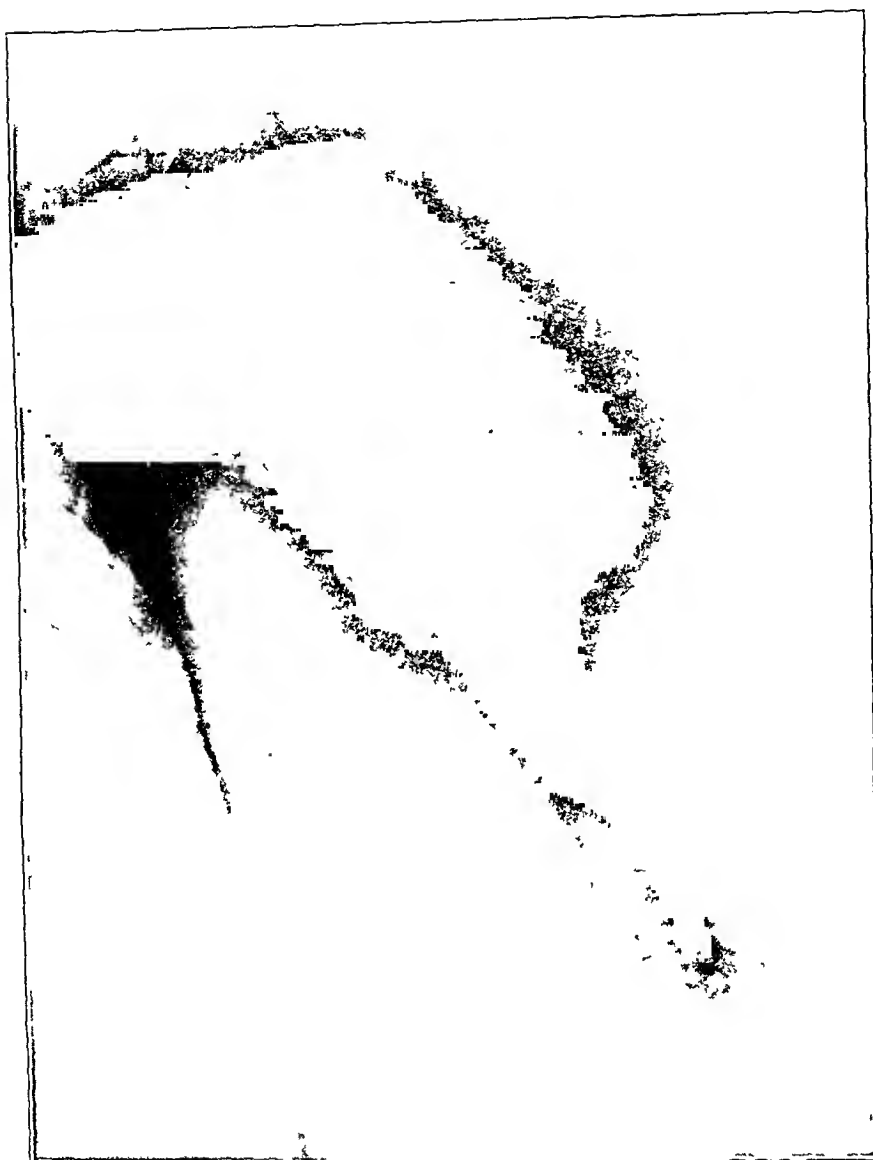


Fig. 60 (P. N. 42888).—Roentgenogram showing beginning malignant change in the upper end of the humerus of a patient who had multiple chondromas of the left hand and a benign chondromatous lesion of the upper end of the humerus. The invasion of the marrow cavity and the pathologic fracture indicate a secondary chondrosarcoma. The patient, who was 50 years old, said that his left arm had always been more crooked and shorter than the right and that the nodules on the left thumb and forefinger shown in the roentgenogram had been present for over forty years. None of these tumors bothered him until two years previously following a fall on the ice. Since that time the upper part of the left arm had been painful, and the swelling there had increased rapidly. A resection of the upper end of the humerus was performed following which the patient died eighteen hours later of postoperative shock.

affected or adjacent bones, and the persistence of the more thoroughly ossified portion of the base or pedicle of the exostosis (figs. 54 and 59).

In advanced cases, the entire tumor site becomes the seat of an infiltrating granular mass in which scattered elements of splintered osseous material may be seen. Destruction of the cortical bone with invasion of the medullary cavity follows, and pathologic fracture may occur (figs. 60, 61, 62 and 63).

The most frequent sources of confusion in the diagnosis of secondary chondromyxosarcoma are benign osteochondromas, myositis ossificans and the sclerosing form of osteogenic sarcoma. The differentiation of this form of chondrosarcoma from a benign exostosis when both are

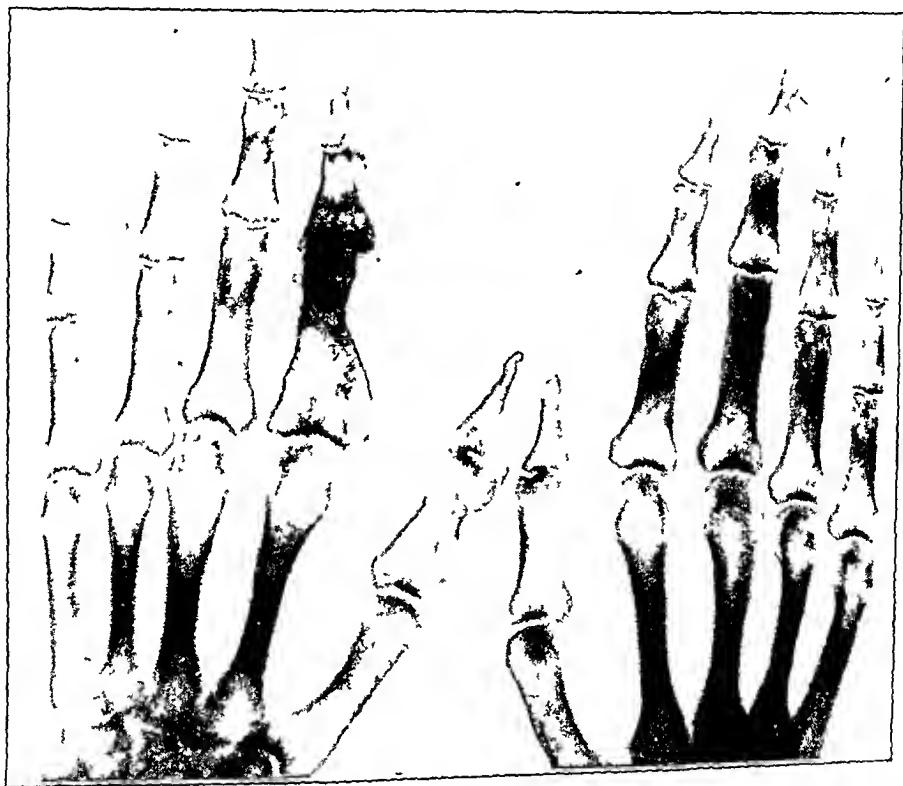


Fig. 61 (P. N. 42888).—Roentgenogram of the hands of the patient shown in figure 61. Note the chondromatous lesions in the left thumb and forefinger.

actually present in the same film is sometimes extremely difficult. The most helpful point is the gradual blotting out of the lines of configuration of the benign lesion from above inward by the malignant change (fig. 54). When the destructive process affecting the bone reaches the medullary cavity, and if pathologic fracture occurs, the diagnosis of malignancy becomes increasingly certain (fig. 60). In myositis ossificans traumatica in which the lesion has been of relatively short duration and has reached a stationary size, the differential diagnosis is not difficult because of the wedge-shaped configuration of the growth and its dense and laminated structure (Lewis¹⁶). But when

the myositis ossificans becomes progressive and the lesion becomes increasingly dense, shaggy and large, it is difficult to tell whether the growth is still benign or whether secondary chondrosarcoma is present (fig. 64). In such cases the lesion is usually malignant, and the diagnosis should be confirmed by biopsy. Sclerosing osteogenic sarcoma



Fig 62 (P. N. 42888).—Gross specimen of the resected humerus shown in figure 60. The cartilaginous tumor mass has invaded the shaft of the humerus and produced pathologic fracture visible at the site of the cystic area in the gross specimen, but shown only poorly in the roentgenogram.

is to be distinguished from this secondary form of chondrosarcoma by the greater density of the periosteal shadow and by the fact that it produces sclerosis of the marrow cavity rather than advanced destruction of cancellous bone.

PATHOLOGY AND HISTOGENESIS

As will be seen from the histogenesis of this group of secondary chondrosarcomas, there is no difficulty in tracing a relationship between



Fig. 63 (P. N. 42888).—Microscopic preparation from the tumor mass shown in figure 63. Note the cellular character of the fibrous tissue separating the chondral lobules. This was a frozen section prepared at operation.

the benign osteochondromas and chondromyxomas and this form of sarcoma of the bone. The real difficulty arises in attempting to differentiate these malignant lesions pathologically from the benign cartilagi-

nous tumors from which they arise and to recognize them as secondary forms of chondrosarcoma as distinguished from the primary form.

In many cases, at the operation or in the gross specimen, the evidence of the original benign growth is plainly visible and will have been inferred from the roentgenogram. This is true in cases in which a benign exostosis, hereditary chondrodysplasia, Paget's osteitis deformans or multiple enchondroma are unquestionably present and the malignancy can be seen as a superimposed change with the more recent and rapid growth surrounding the old and more mature process (fig. 65). From an



Fig. 64 (P. N. 27299).—*A* is a roentgenogram of a typical benign case of myositis ossificans; *B* (P. N. 27702) shows a progressive and invasive case of myositis ossificans in which malignant change is to be suspected.

analysis of the gross specimen and microscopic sections, it can be concluded at once that the previous benign cartilaginous growth is only partly responsible for the more recent and more rapidly proliferating chondrosarcoma. By this is meant that the cartilaginous structure or osteochondral mass built up by the preceding benign neoplastic growth does not undergo transformation into sarcoma as a whole, but instead acts as a fossil remains which is gradually destroyed by the new malignant growth arising from the more primitive connective tissue elements that always persist at the periphery of these tumors.

Histologically, this is evident in an emphatic way. At the site where the sarcoma is arising, there is always a reduplication and proliferation of the connective tissue elements, which are present only in insignificant proportions in the benign cartilaginous group and always interspersed with chondral elements in the primary chondrosarcoma. This proliferation of connective tissue in the secondary chondrosarcoma soon takes on a myxomatous character, and it is because of the conspicuous amount of this myxomatous proliferation present at the margin of these secondary sarcomas that Bloodgood originally called attention to them under the term "pure myxoma of bone" (fig. 66).



Fig. 65 (P. N. 39952).—Gross specimen showing a secondary chondromyxosarcoma arising from the periphery of a benign pedicle exostosis in a colored boy, aged 18. Symptoms referable to the original exostosis had been present for over three years. The patient is living twelve months after amputation of the limb. Note that the fibrocartilaginous sarcoma mass not only extends around the dark pedicle of the exostosis but that it is also present in the bulb or cartilaginous cap of the previously benign growth.

Aside from the relatively large amounts of this myxomatous tissue seen under the microscope, and the evidence of preexisting benign growths often found in the gross specimens, secondary chondrosarcoma differs pathologically in no essential way from the primary chondrosarcomas. From the standpoint of microscopic diagnosis, it is at times

difficult to distinguish both the primary and secondary chondrosarcomas from the closely related benign osteochondromas and chondromyxoma. In general, it is helpful to call attention to the more densely cellular and abundant character of the embryonic connective tissue strands, the interspersed of malignant round cells near these connective tissue strands

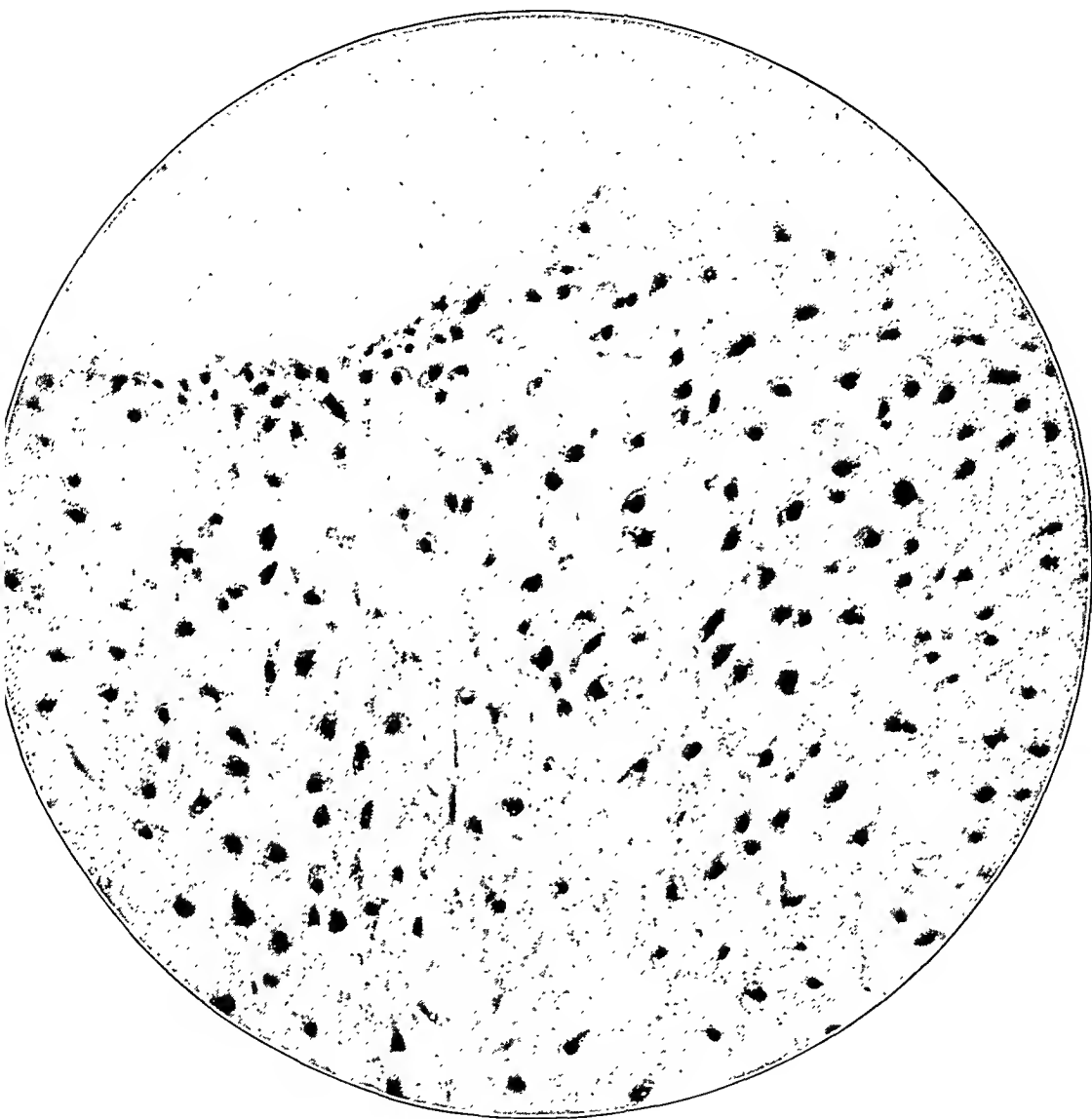


Fig. 66 (P. N. 6773).—Microscopic structure of the lesion shown in figure 54. This portion of the tumor is composed entirely of embryonic precartilaginous connective tissue and fetal cartilage cells, embedded in a hyaline matrix. This is a so-called pure myxoma of bone of Bloodgood.

where they border on myxomatous tissue and the appearance of large multinucleated malignant cartilage cells with mitotic figures amid the chondral lobules, which will be found in the sections of both primary

and secondary chondrosarcoma and absent in benign cartilaginous lesions.

PROGNOSIS AND TREATMENT

When a malignant change has occurred in secondary chondrosarcoma, the average duration of life does not exceed more than two or three years. In a small group of these cases, it is true, the duration may be from four to six years after many recurrences; there are six such cases in this series. In all probability the first recurrence in some of these cases was a benign growth, the malignant change following the recurrence. These secondary malignant tumors grow more slowly than the primary chondrosarcoma and are probably influenced in this matter by the advanced age of the person. If such a tumor is explored and the microscopic section only is submitted for pathologic analysis and prognosis, it is practically impossible to render an accurate opinion because of the gradual gradation from the benign chondromas, on the one hand, and the close resemblance to primary chondrosarcoma, on the other. If

TABLE 8.—*Results of Treatment in Cases of Secondary Chondrosarcoma*

Total number of cases.....	80
Lost	7
Total number of cases followed.....	73
Patients followed less than five years and reported well.....	12
Patients reported dead since 1925.....	11
Number of cases followed less than five years.....	23
Total number of cases followed for more than five years.....	50
Number of patients living over five years.....	12
Number of patients dead previous to 1925.....	38
Percentage of five year cures.....	24%

an x-ray film is available, however, the chances of a cure can be largely estimated by the amount of bone destruction and the extent of the invasion of the marrow cavity by the tumor. The greater the degree of medullary involvement, the worse is the prognosis.

The percentage of actual cures in this form of tumor is 24 per cent (table 8). Of the twelve patients living and well more than five years after treatment, eight were treated by radical resection or amputation. In the other cases, curetting followed by cauterization with the soldering iron and subsequent deep roentgen therapy or radium treatment accomplished a cure. In one of the cases in which a radical resection of the jaw was done after several recurrences following excision, radium was used following the resection.

The remarkable feature in these cases of cure is the effectiveness of radium and the number of recurrences due to ineffective treatment before ultimate recovery was achieved. In one case, which must be looked on as a cure of five years' duration, amputation was performed

four years after the original exploration. In two other cases there were numerous recurrences prior to the amputation or radical resection.

All the patients who were cured except two were over 25 years of age; in two the tumor was at the upper end of the humerus, and in two it extended above the midshaft of the femur. Cures in the upper portion of the humerus or femur speak for low grade malignancy in this type of tumor, since they are extremely rare in this location when the growth is primarily malignant. The actual rôle of the incomplete operation cannot be estimated in any of these cases, since it is possible that the original unsuccessful operations were performed on a benign tumor and a malignant change followed at a later date, closely preceding the final operative procedure. Unfortunately, exact microscopic studies on the tissue from each operation are not at hand to settle this point. However, in view of the many cases that have ultimately proved fatal after recurrences following incomplete operation, it is only fair to assume that radical operation is usually necessary at the outset of the malignant course to effect a cure.

In deciding on the operative procedure, it is well to bear in mind that radium is effective in this form of sarcoma, when complete eradication of the tumor cannot be accomplished by radical resection or amputation. If the tumor is cartilaginous and its benign or malignant nature is in doubt, it is best to excise with the cautery and follow with radium therapy.

CONCLUSIONS

The gradations in a single type of tissue differentiation met with in the osteochondromas (in which bone predominates), in the benign chondroma (in which cartilage predominates) and in the primary and secondary forms of chondromyxosarcoma (in which myxoma and fetal cartilage predominate) seem to imply a close relationship between the formation of tumors and the factors concerned in the growth and differentiation of tissue (table 9).

Apparently all of these various tumors have their origin in a single mother substance, an early precartilaginous connective tissue, and their varying degrees of malignancy are an expression of the rate and extent of differentiation in this tissue. When the rate of differentiation is slow and the extent of cartilage and bone formation is large, a benign exostosis results. When the rate of differentiation is rapid and the amount of adult cartilage and ossification is small, the neoplasms take the form of a chondromyxosarcoma. When an intermediate condition prevails, a benign chondroma, showing a definite tendency to malignant change in many instances, is produced.

In all of these tumors, however, the character of the histogenic cycle is the same, implying that the tissue of origin and not the etiologic agent is the determining factor in this regard. Whether or not the rate and extent of differentiation that governs the degree of malignancy

is predetermined in the tissue at the time of the tumor's origin or whether it is dependent on the etiologic factor precipitating the growth, is difficult to decide. Apparently, however, the etiologic factor is a secondary and variable influence. This is indicated by the fact that the benign exostoses may be accurately duplicated by gonorrheal spurs and arthritic osteophytes of known infectious origin, while similar benign growths such as those in multiple exostoses of the chondrodysplasia type show a definite hereditary tendency. That such widely divergent influences should find expression in a single form of neoplastic process, speaks for the preexistence of a normal growth cycle which may be thus set in motion, and which determines the development and character of the neoplasm.

TABLE 9.—*Leading Clinical Features of Tumors Derived from Precartilaginous Connective Tissue*

Tumor	No. Cases	Age Incidence	Predominant Location	Average Duration of Symptoms	Treatment Recommended	Predominant Microscopic Observations	Average Duration of Life*	Percentage of 5 Year Cures
Exostosis	202	10-25	Lower end of femur; upper and lower end of tibia; upper end of humerus	5 yrs.	None or excision	Adult bone; cartilage	Not affected	95+†
Chondroma	71	20-30	Small bones of hands and feet; ribs; spine	5 yrs.	Curettage with cauterization; radium for recurrence	Adult cartilage	Not affected	95+†
Primary chondromyxosarcoma	79	14-21	Lower end of femur; upper end of tibia; upper end of humerus	6 mos.	Radical excision or amputation and radium postoperatively	Myxoma; fetal cartilage; cartilage and bone	20 months in fatal cases	5
Secondary chondromyxosarcoma	75	35-55	Lower end of femur; upper end of humerus; upper end of femur	6 yrs.	Radical excision or resection and radium implantation	Myxoma; fetal cartilage; cartilage	8-9 years in fatal cases	24

* From onset of symptoms to death.

† There is a definite percentage of malignant change in these cases.

Finally, the fundamental pattern of construction in skeletal tissues (the substitution of connective tissue by cartilage and of cartilage by bone), the order of which is adhered to in evolution, in embryology and in all of the various forms of benign and malignant tumors in the fibrocartilaginous group (fig. 1), indicates an inherent and immutable sequence, which prevails in spite of the avowed lawlessness of tumor growth.

The sequence or order of differentiation that is apparent in this group of tumors of the bone suggests that the formation of the tumor itself is part of the evolutionary process of pattern reproduction, and an expression of the ever present tendency to variation manifested in the derivation of form and pattern throughout the organic world.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.

ROANOKE, VA.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

AND

ADOLPH A. KUTZMANN, M.D.

LOS ANGELES

(Continued from page 174)

BLADDER

Tumors.—Caylor²⁵ stated that so-called papillomas of the urinary bladder should not be considered as benign lesions but as low-grade papillary epitheliomas, for they bear the same relationship to epitheliomas of the bladder as low-grade squamous cell epitheliomas of the lip bear to the more malignant grades of epitheliomas in this organ. The removal of specimens from epitheliomas of the bladder as a diagnostic procedure is important, and the possibility of using diagnoses made from biopsy specimens as a basis for the development of a plan of treatment is emphasized. He also pointed out some salient features of less common malignant lesions of the bladder.

Kretschmer²⁶ reported 109 unselected cases of carcinoma of the bladder in which surgical diathermy was used. There were 87 men and 22 women in the series, the occurrence of carcinoma of the bladder being about four times as common in men as it is in women. Twenty-five patients (22.9 per cent) died in the hospital; 7 patients (28 per cent) died from pulmonary embolism and 4 (16 per cent) from pneumonia; 8 deaths (32 per cent) were the result of urologic complications: anuria caused 3 deaths, suppurative pyelonephritis 3, and uremia 2. In 70 cases, practically two thirds of the series, the condition was

25. Caylor, H. D.: The Pathology of Malignant Bladder Neoplasms, with Especial Reference to the Grading of Epitheliomas, J. A. M. A. **95**:1736 (Dec. 6) 1930.

26. Kretschmer, H. L.: The Treatment of Carcinoma of the Bladder by Surgical Diathermy: A Report of One Hundred Nine Unselected Cases, J. A. M. A. **95**:1728 (Dec. 6) 1930.

far advanced, and the results from the standpoint of cure were highly unsatisfactory; the mortality rate also was high. In 23 cases in which treatment was instituted relatively early, without much involvement of the wall of the bladder, the results were unusually good.

Smith²⁷ studied 50 cases of carcinoma of the bladder, in all of which operation was performed within the last ten years. In 11 cases the growth was excised; 15 patients were treated by electrocoagulation and 24 by the implantation of radium. Nine patients in the last group were treated by electrocoagulation of the tumor before the implantation of radium.

Carcinoma of the bladder may be classified in two groups, the deeply infiltrating and the superficial papillary. In the first group, if the growth has not metastasized or extended beyond the wall of the bladder, it may be excised or destroyed with radium with about a 25 per cent chance of cure. If the growth is situated on the trigone or about a ureter, the chances of success are much less than if it is situated in the dome or lateral wall. For these deeply infiltrating growths, diathermy has not seemed particularly suitable; other methods have been preferable. Tumors of the superficial, papillary type are best treated by electrocoagulation. If the bases of the tumors are indurated, they may be irradiated by the implantation of one or two gold or platinum seeds. Although the immediate mortality in this group was only 7 per cent, the later mortality from recurrence was slightly higher than in the group treated by excision or irradiation.

Barringer²⁸ stated that tumors of the bladder should be classified according to their relative malignancy, so that results can be compared. The papilloma with atypical cells should be regarded as a malignant tumor and so treated. In 127 cases of carcinoma of the bladder in which treatment by radium implantation was given, there were 45 cases of papillary carcinoma, 25 (55.5 per cent) of which were controlled for more than three years. In suprapubic implantation of radium the mortality is between 3 and 4 per cent, whereas in surgical removal the mortality is between 10 and 20 per cent.

Bugbee,²⁹ in a consideration of tumor of the bladder, stated that the medical profession seems willing to consider all tumors of the bladder as potentially malignant. Even the so-called benign papilloma recurs; it grows by direct extension, invasion or implantation, and its

27. Smith, G. G.: The Treatment of Bladder Carcinoma by Irradiation and Diathermy, *J. A. M. A.* **95**:1730 (Dec. 6) 1930.

28. Barringer, B. S.: The Radium Treatment of Cancer of the Bladder, *J. A. M. A.* **95**:1734 (Dec. 6) 1930.

29. Bugbee, H. G.: Discussion of Papers by Kretschmer, Smith, Caylor and Barringer on Tumor of the Bladder, *J. A. M. A.* **95**:1740 (Dec. 6) 1930.

cells have the characteristics of the cells of low-grade epithelioma. This type of tumor responds readily to fulguration and can be kept under control if thoroughly removed and if the bladder is kept under regular observation. From a practical standpoint, tumors of the bladder can be divided into three groups—papilloma, papillary carcinoma and infiltrating carcinoma—with a definite and accepted line of treatment in the first group only.

[COMPILERS' NOTE.—The present concepts of vesical neoplasia are far from standardized. Although efforts are constantly being made to adapt treatment to the type of lesion based on the grading of tissue removed by biopsy, many still treat the tumors cystoscopically on the basis of their gross appearance. As Caylor and Bugbee pointed out, so-called benign papillomas are being more frequently classified as potential epitheliomas. Treatment by fulguration when they are typical of low-grade or border-line malignancy is accepted almost everywhere. In papillary or infiltrating carcinoma, radium, diathermy and surgery compete for precedence in case reports, the ultimate end-results never being satisfactory. However, in the present situation one should not be too critical of any of these efforts at treatment. Total cystectomy for carcinoma of the bladder is offered as a possible means of cure, since the operation of ureteral transplantation is now being placed on a practical clinical basis.]

Schär³⁰ stated that the long inhalation of small amounts of naphthylamine is not only detrimental to the organism, but fatal. The harmful effects of such inhalations may be divided into two groups: generalized toxemia and direct irritation.

With general toxemia there are destruction of blood, anemia, a low hemoglobin content, decreased erythrocytes and removal of blood pigments from the spleen, as well as anisocytosis, poikilocytosis and the appearance of Howell-Jolly bodies and normoblasts. As further evidence of toxemia, there is cloudy swelling of the epithelium in the liver and kidneys, with a heavy central disposition of fat in the liver. There may also be leukopenia and lymphocytosis. Some workers in experimental carcinomatosis had already noted lymphocytosis in the early stages; hence lymphocytosis may be a manifestation in the pre-cancerous stage.

With direct irritation, there is a chronic inflammatory process in the lungs involving the alveoli and interstitial tissues. The kidneys disclose chronic interstitial and proliferative nephritis with cloudy swelling of the epithelium.

30. Schär, Werner: Experimentelle Erzeugung von Blasentumoren, Deutsche Ztschr. f. Chir. 226:81 (July) 1930.

The proliferative reaction with the drug is significant. Certain experimenters have demonstrated malignant changes in the lungs. In some of the experimental animals, a tumor forms in the mucous membrane epithelium of the bladder. This has never been noted in rabbits, probably because they do not live long enough. Schär concluded that processes from papilloma to carcinoma are a direct result of the inhalation of naphthylamine.

Diverticulum.—Briggs³¹ stated that although carcinoma and diverticulum of the bladder are common, carcinoma in a diverticulum or on the dome of the bladder is rare. Deming also observed the infrequency of primary carcinoma in a diverticulum of the bladder. Ten cases have been reported, with 9 deaths. All the patients were men, 8 of whom were in the seventh decade.

Briggs reported a case in a man, aged 73, with papillary tumor of the dome of the bladder, and the sessile base of the tumor was in a shallow diverticulum. The neoplasm, the diverticulum and a wide section of the wall of the bladder were removed surgically. Death occurred on the fifty-fifth day after operation, probably from pyelonephritis.

Gill³² reported a case of carcinoma in a diverticulum of the bladder which was successfully resected. Ten months later the patient was well. He called attention to a rather unusual symptom of diverticula of the bladder in general, which, if it had been considered in this case, might have led to the discovery of the diverticulum before malignancy developed. The patient apparently had been suffering from indigestion for about eight years and had twice sought aid for this trouble. On catheter drainage the feeling of fulness and discomfort in the lower part of the abdomen after eating was entirely relieved. Following operation the patient stated that digestive disturbances disappeared. While the patient was seeking relief from the gastro-intestinal symptoms, signs or symptoms referable to the genito-urinary tract were not present and observers probably gave little thought to the presence of a diverticulum of the bladder as the cause of the abdominal complaint. In making a diagnosis not only the common maladies but the unlikely and rarer lesions that occasionally present themselves should be borne in mind.

Ewell³³ stated that the association of diverticula and a malignant growth of the bladder with secondary involvement of the diverticula

31. Briggs, W. T.: Carcinoma in Diverticulum of the Bladder, *J. Urol.* **24**:517 (Nov.) 1930.

32. Gill, R. D.: Carcinoma in a Diverticulum of the Bladder; Case Report. *J. Urol.* **24**:521 (Nov.) 1930.

33. Ewell, G. H.: Primary Carcinoma in a Diverticulum of the Bladder. *J. Urol.* **24**:649 (Dec.) 1930.

by the malignant process is common. Primary epithelioma of a diverticulum without involvement of the bladder is rare. The diagnosis of a primary malignant process in a diverticulum is not easy unless the tumor can be seen at cystoscopy. A history of hematuria in the presence of a diverticulum is suggestive of malignancy, as well as a demonstrable filling defect in the outline of the diverticulum as shown in the cystogram.

If a malignant process is known to exist in a diverticulum the treatment should be surgical. Hunt expressed the opinion that extirpation of the diverticulum and the growth in the absence of external extension should produce better results so far as cure is concerned than is obtained in primary malignant disease of the bladder. Adequate preoperative treatment with drainage of the bladder is essential to safeguard the patient.

[COMPILERS' NOTE.—Malignant tumors are not uncommon in association with a diverticulum. The infection and inflammation and the occasional irritation from calculi are apparently conducive to the formation of new growths, as the incidence of association of diverticulum and carcinoma is high. Targett described three cases from London museums; in one case the diverticulum contained a large sarcoma, in another a papillomatous tumor, and in the third an epithelioma which grew into the diverticulum from the wall of the bladder. Young reported a case in which a carcinoma was found protruding from a peupoint orifice of the diverticulum. Hofmohl reported a case of a large single diverticulum filled with polypi.]

Lower³⁴ stated that diverticula in the urinary bladder are usually situated in the lateral wall near the ureters. The diverticulum was in the lateral wall in 62.1 per cent of a series of 151 cases; it was on the posterior wall in 21.2 per cent, rarely in the dome and seldom in the trigone. Diverticula may occur at any age, but they usually occur after the age of 50, as in 81.3 per cent of Lower's 151 cases.

Many cases of calculi associated with diverticula have been reported; the stones may be in the bladder, in the diverticulum or in both, or a dumbbell-shaped stone may lie partly in the bladder and partly in the diverticulum. Malignancy is not a rare complication. In 8 cases of the series a diverticulum was associated with tumor of the bladder, and in 2 of these cases, a papilloma was present in the diverticulum.

Complete excision is the only procedure that leads to permanently satisfactory results. In the reported cases the operative mortality varied from 6 to 8 per cent. In Lower's series, in which excision of

34. Lower, W. E.: Diverticula of the Urinary Bladder, *Surg. Gynec. Obst.* 52:324 (Feb. 15) 1931.

the diverticulum was performed, the operative mortality was slightly more than 5 per cent. In a few of the earlier cases, there has been recurrence and a second operation has been performed.

If a radical operation is performed early and before renal impairment has become marked, the prognosis is usually favorable. Whether there will be a recurrence of the diverticulum depends partly on the manner in which the opening into the bladder is closed after the diverticulum is removed, and in part on whether the obstruction to the urinary outflow is eliminated. If the musculature is not well approximated, or if any defect remains, this may be the starting point for a recurrence.

Walters and Mulholland³⁵ stated that there are three methods of resecting diverticula of the bladder. The first two methods are mainly intravesical operations. In one method the diverticulum is inverted and cut off, and the opening is sutured; the other method is similar, except that a purse-string suture is placed about the neck of the diverticulum before inversion. The third method is by extravesical dissection. Diverticula of the bladder are almost always attached to the adjacent ureter. In order to avoid injury to the ureter it should be remembered that the vesical orifice of the ureter is in close proximity to the opening of the diverticulum into the bladder. All diverticula are associated with definite obstruction of the vesical neck. If the patient is young, the obstruction may be due to cicatricial urethritis; if he is old, it usually is due to hypertrophy of the prostate gland or to a median bar.

Syphilis.—Ajamil³⁶ reported a case of vegetative syphiloma of the bladder. The capacity of the bladder was small, and when the cystoscope was turned toward the trigone the bladder was found to be hidden completely by a papillomatous mass which extended from the base of the bladder to the neck and to the lower part of the urethra. The remainder of the bladder was only slightly congested around the vertex and lateral walls. Lesions of the trigone were formed by a number of pointed papillae which were set close together; they were slightly transparent in some places, closely resembling intense bullous edema, with a characteristic slight slough on the apex of some of the papillae. The Wassermann reaction of the blood and the Kahn test were negative twice, but examination of the spinal fluid disclosed syphilis.

On the basis of this positive result a final diagnosis of vegetative syphiloma of the bladder, concomitant with prostatic syphilis, was

35. Walters, Waltman; and Mulholland, S. W.: Diverticulum of the Bladder: Report of Six Cases, *Proc. Staff Meet., Mayo Clin.* 5:347 (Dec. 3) 1930.

36. Ajamil, L. F.: Vegetative Syphiloma of the Bladder, *J. Urol.* 25:53 (Jan.) 1931.

made. Thirty centigrams of neoarsphenamine was injected intravenously. Two days later all vesical symptoms had decreased noticeably; the dysuria and pollakiuria had almost disappeared, the urine was less purulent, and the fever was lower. Three days after the injection cystoscopy revealed that all the papillomatous lesions had disappeared; only slight congestion of the surface of the trigone and vesical neck remained.

Stone.—Mombaerts³⁷ attempted to ascertain by experimental study why approximately 50 per cent of stones of the bladder are not detected in the roentgenogram, whereas only 1.2 per cent of stones of the kidney (Arcelin) are not detected in the roentgenogram. Regardless of their composition, all stones of the bladder, if examined roentgenologically outside of the body, produce definite shadows. The opacity of a stone is a function of its atomic weight and of its thickness. Density interferes only rarely; a dense stone made of uric acid is less opaque than a porous stone of calcium phosphate. The projection of the shadow of stone on the pubic shadow does not make it less visible. A slight displacement of the shadow during the pose considerably diminishes its visibility. Liquid in the bladder markedly lessens the shadow of a stone. If stones are put into water and examined by roentgen rays the most opaque ones become indefinite in contour, whereas the less opaque ones disappear. Shadows of any stone will not appear if the quantity of liquid is sufficient, whether it is normal urine, bloody or purulent urine or distilled water. In examination of a full bladder, the most penetrating rays will give better results. Soft parts play the same rôle as water. If the bladder can be filled with air, the opaque stones cast a better shadow. This procedure is not always simple; it is not always reliable and is sometimes harmful. If the bladder is filled with colloidal silver, the slightly opaque stones show better but the others disappear. It is Mombaerts' conclusion that before a roentgenogram is made the bowel should be empty, opium should be used to quiet peristalsis, enemas which may leave water in the rectum should be avoided, the patient should stop breathing, pressure should be applied on the bladder and it should be emptied completely.

[COMPILERS' NOTE.—It is well known, yet worthy of emphasis, that in a considerable number of cases the plain roentgenogram fails to reveal the presence of vesical calculi of considerable proportions. Every cystoscopist is occasionally surprised to find an unsuspected stone which the plain roentgenogram failed to reveal. Mombaerts' explanation of

37. Mombaerts, Jean: Pourquoi certains calculs de la vessie sont-ils invisibles à la radiographie? *J. d'uro.* 28:113 (Aug.) 1929.

this fact is timely and the preparation of the patient and the technic of exposure that he advised are worthy of trial.]

Neurosis.—Hunner³⁸ stated that one of his chief contributions toward the solution of the problem of neurosis of the bladder is insistence on a personal study of the urine. In certain cases there may be extreme discomfort of the bladder, with pain reflected to the pelvis and lower part of the abdomen, frequency of urination and nocturnal and diurnal incontinence, although urinalysis may yield negative results and cystoscopy reveal nothing but urethritis or urethritis associated with trigonitis. In more than 200 cases of elusive ulcer, there were 4 or 5 in which, after years of intermittent treatment, symptoms ceased even though the cystoscopic picture was similar to the one present for years. In about the same number of cases healing had apparently been complete. Cystoscopic examination did not reveal a trace of inflammation except the white scars of former ulcerous areas, and the urine was normal.

One of the simplest methods of effective treatment for elusive ulcer is the instillation of a 1:500 solution of silver nitrate twice a week, 30 cc. being left in the bladder. Some patients obtain more relief from the direct application to the ulcerous area of a 10 per cent solution of silver nitrate. In many cases the relief lasts for four or five weeks, when symptoms become worse and require another treatment. Hunner preferred fulguration under complete narcosis when simpler devices fail to give satisfactory relief. In most cases benefit from this treatment lasts from six months to two years.

It is probable that the ulcer recurred in 6 of 25 cases in which operation was performed; time will probably show a large percentage of recurrence. In his series of 137 cases of elusive ulcer, operation was performed in 48. One patient died as a result of inefficient care after operation and 26 patients (42 per cent) were known to have recurrence. He had not performed operations for this condition since gathering these statistics.

In 100 consecutive cases of ureteral stricture, vesical symptoms were present in 71. In 33 of these the symptoms were marked and more or less constant, and in 38 they were mild. Many of the patients had rather severe vesical symptoms during attacks of renal pain owing to partial or complete closure of the stricture. In a series of 100 cases of ureteritis, infiltration of the urethra occurred in 85.

In more than 250 cases of partial or complete incontinence, ureteral stricture was usually found to be the cause. Good results have been obtained in most cases by restoring good drainage of the kidney or

38. Hunner, G. L.: *Neurosis of the Bladder*, J. Urol. **24**:567 (Dec.) 1930.

by the elimination of distant focal infection. Excellent results followed the treatment of nocturnal incontinence of children by tonsillectomy.

Dermoid Cyst.—Kalo³⁹ noted the rarity of dermoid cysts of the bladder. The literature reveals that they may occur in almost any organ, but they usually occur in the ovary and adjacent regions. Kalo reported a case in which he expressed the belief that the cyst originated in the right ovary. The patient, a woman, aged 57, had had urinary difficulty for many months. The urine was cloudy and infected. It became clear following irrigation of the bladder. It contained droplets of cholesterol-like substances. Above the right ureteral orifice was an opening from which came cloudy turbid material, as well as hair; this was especially pronounced on suprapubic pressure. A cystogram revealed a shadow about 7 cm. in diameter to the right of the bladder. A tumor was removed at operation; it was 5 by 7 cm. and contained bone and hair. Evidence of malignancy was not found.

Kalo noted only two similar cases in the literature. Delore and Alimartin reported a case of left ovarian origin in a woman, aged 58. Rejschek reported a case in a woman, aged 37. Kalo stated that the invasion through the wall of the bladder might be considered as evidence of malignancy, although microscopic evidence of malignancy was not found.

Appendiceal Fistula.—Chauvin⁴⁰ reported a case of cecovesical fistula of simple inflammatory origin. This lesion is much less common than fistulas of tuberculous or neoplastic origin. Inflammatory fistulas often permit complete and satisfactory surgical treatment, that is, suture of the bladder and of the intestine after resection of the fistulous tract. Appendicitis is the most common cause of inflammation; it was the cause in 4 of 23 of Albano's cases of nontraumatic fistula, in 6 of 32 of Pristavescio's cases, in 3 of 57 of Douglas' cases, and in 9 of 292 of Pascal's cases. The abscess of the appendix may unite a mass of intestinal loops and these may be in contact with the bladder; consequently, the communication between the bladder and the intestine may be found far from the ileocecum. The diagnosis of this disease is simple when three characteristic symptoms are present: (1) the transit of fecal matter into the bladder or the presence of urine in the bowel, (2) pneumaturia or (3) a fistulous opening in the bladder discovered at cystoscopic examination.

39. Kalo, Andreas: In die Blase perforierende Dermoidcyste, Ztschr. f. Urol. **24**:330, 1930.

40. Chauvin, E.: Fistule caeco-vésicale d'origine appendiculaire, Bull. et mém. Soc. nat. d. chir. **56**:559 (April 9) 1930.

[COMPILERS' NOTE.—Fistulas may arise between the bladder and rectum, colon, ileum, cecum or appendix. Trauma during operation or accidental injury may be the cause. Inflammatory rupture from the viscus into the bladder may occur. More often tuberculosis or neoplasia is responsible for the spontaneous development of fistula. Pascal, Craig and Lee Brown, and Bryan have written extensively on the subject. Rectovesical fistula was found in 135 of 195 cases. Separation of the bladder and intestine with suture is usually followed by good results in the absence of tuberculosis and actinomycosis. The prognosis in cases of neoplasia depends on whether the tumor can be resected completely.]

PROSTATE GLAND

Hypertrophy.—Thomson-Walker⁴¹ stated that when McGill first advocated the suprapubic operation for prostatectomy, it was generally accepted that about 30 per cent of all men more than 55 years of age had abnormally large prostatic glands, but that only about 50 per cent of them had significant symptoms. Unless there was frequency of urination due to infection of the bladder or partial or total retention of urine, the enlargement of the gland might be disregarded. Infection and retention demanded surgical aid, which was afforded by the occasional or the habitual passage of the catheter. Patients with enlarged prostate glands were taught to pass a soft catheter and were instructed to pass it once or twice a day. The introduction by Mercier of the coudé or curved gum-elastic catheter was to be a great step in treatment in these cases. The cumbersome mahogany case holding catheters was eliminated, and patients carried one catheter in their walking-sticks or umbrella-sticks.

Treatment with a catheter was not always successful. In certain cases the difficulty of a much distorted prostatic urethra or the inability of the patient to learn to pass the catheter prevented the adoption of this method. In acute retention of urine a metal catheter might be forced through the obstruction, tearing through the gland and forming a new channel. Tapping the bladder with a metal trocar and cannula above the pubes, in the perineum or through the rectum, was the common method of treatment.

McGill noted three cases in which suprapubic operation had been successfully performed for chronic prostatic hypertrophy. The operation consisted of opening the bladder and removing that portion of a hypertrophied prostate gland which prevented the passage of the urine from the bladder into the urethral canal.

41. Thomson-Walker, John: Enlarged Prostate and Prostatectomy, *Lancet* 1:1163 (May 31) 1930.

Gouley, of New York, was the first to formulate a plan for perineal prostatectomy. The intravesical enlargement of the prostate gland is first explored through an external perineal urethrotomy wound. If a median outgrowth or isolated tumors are discovered, the prostatic urethra is dilated and incised laterally and the outgrowths are removed, preferably by an *ecraseur*. Harrison recommended a similar operation with subsequent prolonged drainage.

White noted that in about 20 per cent of cases following suprapubic prostatectomy the bladder does not regain power. He considered that possibly the analogy between uterine fibromyoma and prostatic overgrowth is a real one. Castration might have the same effect on the latter that oophorectomy has on the former, and cause shrinkage or atrophy that would result practically in the disappearance of the obstruction. He did not have the courage of his convictions and never seriously recommended the operation. Others acted on his hypothesis and the operation of castration as a method of treatment for prostatic obstruction was practiced generally.

The mortality caused by suprapubic prostatectomy in McGill's 24 cases was 16.6 per cent. Belfield, in 1890, placed the mortality from the operation at 13.6 per cent. The mortality after castration, which White had expected would be negligible, was 19.4 per cent.

The renaissance of prostatic surgery occurred during 1900 and 1901. Prostatectomy, both by the perineal and by the suprapubic route, found new advocates, and expanded to become the accepted method of treatment for prostatic obstruction. The handicap of the perineal operation had been the difficulty of reaching the gland by this route. In America, Young had been the chief advocate of the perineal operation, and it is due to his advocacy and fine record of results that perineal prostatectomy retains a place among American surgeons. In 1901, Freyer reported four cases in which he operated for radical cure of the enlarged organ by total extirpation. The method described by Freyer was at once adopted by surgeons all over the world.

As a result of watching these cases and from his own experience, it seemed to Thomson-Walker that hemorrhage, if not the direct cause of death in many cases, is a predisposing factor. Although the removal of the prostatic urethra was usually not attended by the risk of traumatic stricture, there were, unfortunately, numerous exceptions; the traumatic stricture of the urethra that followed prostatectomy was difficult to treat. Thomson-Walker also realized that among other points in technic a clean cavity, without capsular shreds or partly detached masses of prostatic tissue and mucosa, was necessary in order to prevent persistent infection after the operation. Keeping in mind the defects of Freyer's operation, he introduced (1916) a method of open operation,

in the hope of preventing the occurrence of such complications. He has used the method in an increasing number of cases until it has become his routine practice. The operation avoids placing the finger in the rectum, and hemorrhage is controlled by free exposure and ligature. All tags, flaps and nodules that might cause sepsis or post-operative obstruction are removed, and the prostatic vesical orifice is opened to prevent contraction.

Chynoweth⁴² stated that in a study of 500 patients with urologic disorders, aged from 28 to 84 years, approximately 70 per cent had some form of prostatic disease. Of these 70 per cent, 60 per cent gave a definite history of venereal disease and almost 10 per cent had infections of the teeth or tonsils or both. Two or more pus cells to the field were found in approximately 60 per cent of the prostatic smears. In 12 per cent of these cases a diagnosis was made of simple congestion of the prostate gland. The ages of the patients ranged from 28 to 45. In 50 per cent of the cases benign prostatic hypertrophy was sufficient to cause urinary retention; in 12 per cent retention was complete. Of the cases of prostatic hypertrophy 53 per cent were extravescical enlargement, palpable by rectal examination; 20 per cent were combined intravesical and extravescical enlargement, determined by cystoscopy and rectal examination; 10 per cent were of the intravesical type, as ascertained by cystoscopy and rectal palpation, and 12 per cent were bar obstructions with or without involvement of the lateral lobe. Prostatic bar enlargement is usually associated with fibrosis at the neck of the bladder. In 5 per cent of the series of 500 cases the condition of the prostate gland was malignant.

The size of the gland as determined by examination of the rectum and prostate gland does not always indicate the degree of obstruction produced and does not give complete information as to the condition of the gland. Certain adenomas grow rapidly and produce obstruction; others grow gradually. In this series 22 per cent of the prostate glands were found to be normal by rectal palpation; in 20 per cent the enlargement was noted by cystoscopic as well as by rectal examination.

As a rule, in the presence of persistent residual urine of 60 cc. or more, the prostatic condition tends to progress, and surgical procedures are indicated in most cases. If surgical treatment is indicated it should be undertaken before renal function is impaired. A comparatively simple operation if not done in time may be dangerous. Interference with renal function means inefficient elimination of waste

42. Chynoweth, W. R.: Prostatic Obstruction Caused by Intra-Extra Vesical Hypertrophy; Review of 500 Cases, *J. Urol.* **24**:669 (Dec.) 1930.

products and favors toxemia which affects all tissues of the body, inducing the final stage of uremia.

Spinal anesthesia was chosen for 90 per cent of the prostatectomies, thus minimizing postoperative renal depression, gastro-intestinal distress and pulmonary complications. In the other 10 per cent of cases gas anesthesia was used.

Gibson⁴³ stated that primary closure and healing are applicable to wounds of perineal prostatectomy, and that closure can be made the rule rather than the exception. Gauze packs or distensible rubber bags for hemostatic purposes both offer a number of objections: They stretch open still farther the dilated prostatic cavity, which under ideal conditions should be permitted to collapse and shrink as soon as the gland is removed; they cause the patient discomfort, not only by their presence but by their removal, and they delay healing by leaving, on their withdrawal, a temporary urinary fistula, which requires ordinarily from two to four weeks to close.

Before primary closure can be done safely, all bleeding must be carefully controlled. The wound can then be closed tight without drainage, the urinary stream being taken care of by means of a retention catheter through the urethra. If bleeding cannot be checked satisfactorily by suture, the prostatic fossa must be packed with gauze strips.

In perineal prostatectomy it is generally possible to get an adequate view of the neck of the bladder, and in most cases closure can be made without either packs or bags. In a consecutive series of 20 cases of perineal prostatectomy Gibson made a primary closure successfully in 13. In the other 7 cases he was compelled to resort to packs to check the bleeding completely. Analyzing the two groups of cases with respect to the duration of postoperative convalescence, the average time spent in the hospital by patients for whom packs were used was twenty-two days. In cases of primary closure in which packs were not used the average time in the hospital after operation was sixteen days.

[COMPILERS' NOTE.—Young described a technic of primary closure in perineal prostatectomy. Lower and Harris adapted primary closure to the suprapubic operation with reasonable success. Gibson, independently of Young, developed a similar technic. In spite of the theoretical arguments in favor of primary closure as an ideal procedure, it is slow in gaining popularity. Reconstructive operations that tend to obliterate the prostatic fossa after prostatectomy are difficult of application, and the end-results of even the most enthusiastic advocates of the method are not consistently good. At best, Gibson saves less than

43. Gibson, T. E.: Primary Closure in Prostatectomy. *Ann. Surg.* 92:82 (July) 1930.

a week in the hospital in about 60 per cent of his cases, and avoids some transient pain. We consider the operation of primary closure an ideal objective but still in the developmental stage. Much more clinical experience with the procedure will be necessary to give it proper evaluation.]

Carcinoma.—Colston⁴⁴ divided carcinoma of the prostate gland into three groups: 1. Cases suitable for radical operation. Since carcinoma of the prostate gland in the earliest stages does not cause symptoms, the cases in this group are few. The growth may be comparatively small and limited to the gland. If a radical operation is to be performed satisfactorily the growth must not have extended beyond the capsule, into the seminal vesicles or to the base of the bladder.

2. Cases of carcinoma without obstruction, in which the growth has extended usually upward into the seminal vesicles and pelvic lymph-nodes, or to the base of the bladder. Metastasis to the bones of the pelvis or lumbar spine may or may not be present. Patients with this type of growth are best treated by a combination of radium and roentgen rays. In many of these cases, death from cachexia and widespread metastasis may occur with little if any increase in the size of the original tumor.

3. Cases with more or less urinary obstruction, with or without metastasis to bone. Conservative perineal prostatectomy or the punch operation are best in these cases. Of 268 cases of carcinoma of the prostate gland seen at the Brady Clinic between 1922 and 1927, the conservative perineal prostatectomy was performed in 107, the punch operation in 25 and the radical operation in 13; radium and roentgen rays were used in 65, and in 56 treatment was not given.

Conservative perineal prostatectomy is carried out under caudal anesthesia, which has resulted in a decrease in the mortality. In the 107 cases there were 8 operative deaths (7.5 per cent), about twice the mortality in the benign cases. It was noted that deaths from pneumonia occurred before caudal anesthesia was used as a routine measure. Of the 99 patients who survived operation, only 34 have been traced; 13 of the 34 died within a year after operation, 8 died within two years and 1 died four years after operation. One patient is living, without symptoms, seven years after operation, another is living six years, another five years, another three years, and 8 patients are living two years, after operation; 4 of these 8 are without symptoms, 1 has partial incontinence and 3 have slight frequency and occasional hematuria.

44. Colston, J. A. C.: Treatment of Urinary Obstruction Due to Malignant Disease of the Prostate, *J. Urol.* 24:656 (Dec.) 1930.

The postoperative course is approximately the same as in benign cases. A catheter is usually left in the urethra and withdrawn about the tenth day. There is a varying degree of incontinence which may persist for several weeks after urethral voiding has been reestablished. Of the 12 patients living more than two years after operation, only 1 has partial incontinence.

The ultimate outcome in malignant disease of the prostate gland is poor. In a certain proportion of cases a lasting functional result can be obtained which will restore the patient to a comparatively normal life, and no other operative procedure will give such satisfactory results as perineal prostatectomy. If left alone, these patients die of urinary obstruction, and if subjected to suprapubic cystostomy, invalidism is the result.

Sarcoma.—Raap⁴⁵ stated that in 50 per cent of the reported cases of sarcoma of the prostate gland surgical treatment was given. Kretschmer found 80 cases of sarcoma of the prostate gland previous to 1926. Deming, in 1924, collected 65 cases with an extensive bibliography, and stated that sarcoma was present in about 56.9 per cent. The classification included sarcoma, myxosarcoma, fibrosarcoma and lymphosarcoma. Myxosarcoma constituted 25 per cent of the cases, fibroma constituted about 7 per cent, and there was an occasional myoma, rhabdomyoma, fibroma, papilloma, polyp and dermoid. Angiosarcoma and chondrosarcoma have also been reported.

Albarran found that of 252 primary tumors of the bladder, 211 occurred in males and 41 in females; only 6 of the patients were less than 10 years. One of the youngest patients, a girl aged 11 months, had a sarcoma in the bladder. This case was reported by Concetti.

Raap reported the case of a boy, aged 4 months, with urinary retention for one month. Catheterization revealed a grating obstruction in the posterior urethra. On rectal examination a tumor in the prostatic area was definitely outlined. Suprapubic cystotomy was performed. The patient died several weeks later and necropsy revealed extensive prostatic myxosarcoma, together with bilateral hydronephrosis and hydro-ureter.

[COMPILERS' NOTE.—In Young's opinion the condition is rare, and primary sarcoma of the prostate gland is frequently mistaken for sarcoma arising in the retroprostatic tissues. A satisfactory method of treatment has not been found. Palliation by surgical procedures or roentgenotherapy is preferred at present.]

45. Raap, Gerard: Sarcoma of the Prostatic Area in an Infant Aged Four Months; Case Report, *Am. J. Roentgenol.* **24**:185, 1930.

PENIS

Carcinoma.—Mauclaire⁴⁶ stated that in the diagnosis of carcinoma of the penis syphilis must always be considered. The technic he advocated in 1903 was the complete extirpation en bloc of the tumor, of the principal superficial lymphatic territory and of the inguinocrural glands on both sides. In the benign forms, the inguinocrural glands are often inflammatory. Majaux stated that these glands are neoplastic in from 30 to 40 per cent of the cases. In some malignant forms complete extirpation of the lymphatics is justified. In such cases, as in cases of carcinoma of the breast, operation should include complete extirpation of the infected regions, tumor, principal superficial lymphatics and bilateral nodes. The deep lymphatic vessels of the breast must be left in place. Complete extirpation of inguinocrural glands necessitates a large wound and sometimes troublesome scarring. The wound often suppurates. Packing the wound instead of suturing is advocated. Mauclaire stated that elephantiasis may develop in the upper part of the thigh after removal of the lymphatics.

Ferry⁴⁷ reported a case in a man aged 78, who had a carcinoma of the penis following an operation for phimosis and balanitis. The tumor was treated by radium; the cure was rapid and has been maintained for four years. Monod, in discussing this case, stated that carcinoma of the penis is a rare lesion in France, representing only from 2 to 3 per cent of all carcinomas, and affecting only patients who had suffered from phimosis. In India and Indo-China, this lesion is more common, comprising 17.5 per cent of all carcinomas. The significance of phimosis as a cause is also demonstrated by the fact that the disease is almost totally absent among Mahometans. Syphilis is also a cause of carcinoma of the penis. Le Roy des Barres, who has had much experience in the matter, has observed it in 50 per cent of cases. The lesion of syphilis resembles epithelioma of the skin. Its evolution is slow, taking three years as an average, although Ferrari has reported cases of twenty years' duration. Recurrence is common, but localized. Distant metastasis is rare. Enlarged inguinal lymph nodes, often inflammatory, have been found in 70 per cent of cases; in Monod's cases they have always been noncarcinomatous.

Two methods of treatment may be used: operation and roentgenotherapy. The surgical treatment consists in removing the tumor, care being taken to amputate as little of the penis as possible. It is still

46. Mauclaire: À propos du traitement du cancer du pénis, *Bull. et mém. Soc. nat. d. chir.* **56**:710 (June 7) 1930.

47. Ferry, G.: Les indications thérapeutiques actuelles du cancer de la verge: À propos d'un cas guéri depuis quatre ans et demi, *Bull. et mém. Soc. nat. d. chir.* **56**:618-627 (May 14) 1930.

undecided whether the inguinal lymph nodes should be removed. Le Roy des Barres does not remove them. Biopsy may be performed and, if necessary, the nodes can be removed later; often this will not be necessary. In the opinion of Ferry, Ferrari and Le Roy des Barres, but contrary to general opinion, roentgenotherapy gives excellent results in carcinoma of the penis. Radium usually leaves a normally functioning organ. From the Institut du Radium the following statistics are noted: The end-results were traced in 16 cases. In 9 cure was complete; in 1 case there was improvement and in 5 cases failure; thus cure was obtained in 60 per cent of cases, lasting from three to eleven years. The surgical statistics from Legueu and Kuttner, in 1908, at the International Congress of Surgery give only 30 per cent of cases without recurrences (traced less than four years).

[COMPILERS' NOTE.—A fair opportunity for cure of carcinoma of the penis is afforded by surgical procedures or the application of radium if the lesion is recognized early. Increasing evidence is available to show the superiority of radium treatment if applied properly, and before the growth has penetrated Buck's fascia or metastasized to the inguinal or possibly to the deep pelvic lymph-nodes. The articles of Mauclaire and Ferry bring out the factors to be considered in the use of surgery and radium. Whether the inguinal glands are to be dissected out is a moot point. Those advocating radical operation will certainly feel that biopsy which shows definite metastasis would be an indication for radical dissection. Advocates of roentgenotherapy believe that this form of treatment is sufficient, that it maintains function of the organ and more cures for three or more years.]

TESTIS, EPIDIDYMIS AND SEMINAL VESICLE

Tuberculosis.—Felsenreich⁴⁸ stated that the treatment for tuberculosis of the epididymis is still an important problem. Several methods of treatment are employed: the radical method, castration and semicastration; a conservative operation, partial or complete epididymectomy, curetting or incision; roentgen therapy, and the conservative regimen with sunshine and similar measures.

There were 235 proved cases of tuberculosis of the epididymis. One hundred ninety-seven of the patients were observed after operation and carefully traced. Three methods of treatment were used: operative, such as semicastration, castration, and epididymectomy; roentgenotherapy, including roentgen rays and sunshine; injections of iodine compounds, and baths and compresses.

48. Felsenreich, Fritz: Die Therapie der Nebenhodentuberkulose und ihre Fernresultate, Deutsche Ztschr. f. Chir. 224:383, 1930.

There were 61 cases in the first group. Three years after operation 45 per cent of the patients were free from recurrence. Most recurrences occurred within the first three years after operation.

There were 50 cases in the second group. The patients were given roentgen treatment. It was found that frequent small doses were most satisfactory, the temperature, general reaction, increased pain and swelling being utilized as indicators of the treatment. In 34 cases, 32 per cent of the patients were free from recurrences; in 26 per cent recurrence developed within three months and in 42 per cent it developed later. In this group 8 patients died, 6 from pulmonary tuberculosis and 2 from miliary tuberculosis. From the results in these cases Felsenreich stated the belief that better results could be obtained with roentgenotherapy in the presence of severe pulmonary involvement than with surgical procedures.

The third group consisted of 38 cases. Most of the treatment consisted of conservative local measures, such as the use of iodine ointments and sunlight. The severest cases were included in this group and the mortality was 40 per cent within the first two years of observation. In the entire series, patients who died or who had recurrence had pulmonary tuberculosis. Felsenreich concluded, with Bier, that surgical tuberculosis affects the entire body, that it is in reality metastasis in most cases. The consideration of surgical tuberculosis must be preceded by the study and care of the entire organism.

Tumors of the Testis.—Champlin⁴⁹ stated: "Similar tumors in identical (uniovular) twins have been reported rarely. Similar disease has been observed in twins more frequently. It is reasonable to suppose that fetal rest tumors especially could occur in both of uniovular twins. The identical twins presented here both developed sarcoma of the right testicle—fatal in one on account of delay in treatment and in the other apparently cured by early removal."

Sterility.—Hagner⁵⁰ considered sterility of the male mainly from the standpoint of operative correction. In most cases failure of impregnation is due to the female. Statistics show that the male is at fault in about 1 case in 6.

Sixty-seven operations were performed in 55 cases. Twelve patients were operated on a second time because of initial failure; 7 of the 12 were cured by the second operation. The results in 4 of the 55 cases were not reported. The condition of 20 patients was discovered at

49. Champlin, H. W.: *Similar Tumors of Testis Occurring in Identical Twins*, J. A. M. A. **95**:96 (July 12) 1930.

50. Hagner, F. R.: *Sterility in the Male*, Surg. Gynec. Obst. **52**:330 (Feb. 15) 1931.

the exploratory operation to be inoperable because of occlusion of the vas or absence of spermatozoa in the epididymis. Of the remaining 31 patients, 19 (61.3 per cent) were cured, including the patients reoperated on; 12 of the 19 patients cured became fathers of from one to six children, and in 1 case impregnation was followed by a miscarriage.

Calcification of the Vasa Deferentia.—Bianchini⁵¹ reported the case of a man, aged 34, who complained only of hematuria; he had no other subjective or objective symptoms. The roentgenogram showed almost complete calcification of the vasa deferentia. The patient was not syphilitic and had been well up to the age of 19, when he had tuberculous epididymitis and a local cold abscess was opened. This and general systemic treatment effected a cure. He had been married for thirteen years, and his wife had had an abortion in the fifth month ten years before examination. Eight years before examination she had a child, who was living and well. Bianchini believed that the tuberculous epididymitis caused the almost total calcification of the vasa deferentia. Obstruction of the vasa deferentia had developed slowly; it had not become complete until recent years.

ANESTHESIA

Bumpus⁵² stated that the use of spinal anesthesia became more general as a result of the development of less toxic drugs than cocaine. Delaup, in 1910, reported 1,239 cases; in 585 cases, operation was for genito-urinary conditions. Richards, in 1911, reported 500 cases, in 219 of which operation was required for urologic conditions. Pauchet, in 1913, stated that he had used spinal anesthesia in 300 cases for prostatectomy; that it decreased hemorrhage, gave complete abdominal relaxation and rendered enucleation easy. The same year Morrison reviewed 1,295 operations, many of them performed for urologic conditions, including 43 operations on the kidneys, and noted that the danger incidental to spinal anesthesia was in lowering the blood pressure. Chute, in 1922, reported 328 cases of prostatectomy in which he employed spinal anesthesia without serious complications attributable to the anesthetic. Labat emphasized that the danger of spinal anesthesia is not from the fall in blood pressure, except when it produces cerebral anemia, but is attributable to the increased volume of blood in the viscera, due to splanchnic paralysis and vasomotor collapse. He expressed the belief that this cerebral anemia can be avoided by placing the patient in the Trendelenburg position immediately following the

51. Bianchini, A.: Su di un caso di calcificazione quasi total delle vie deferenziali. *Arch. di radiol.* 6:228 (Jan.-Feb.) 1930.

52. Bumpus, H. C., Jr.: History of Regional Anesthesia in Urology. *J. A. M. A.* 96:83 (Jan. 10) 1931.

intraspinal injection. Keyes, in 1928, stated that spinal anesthesia is admirably suited to all operations on the bladder. For five years he had used capsules containing 120 mg. of procaine hydrochloride crystals, without fatalities.

The first attempts at prostatectomy under parasacral anesthesia were made in 1907. Farr experienced failure in 10 per cent of cases when the method was used for perineal and rectal operations. He supplemented parasacral anesthesia with local infiltration which, in the case of prostatectomy, had to be extended to the capsule.

Stoeckel, in 1909, published the results of a series of injections into the sacral canal during labor, and called the method sacral anesthesia. Lewis, in 1916, reported 85 cases in which he had used sacral anesthesia, with failure in 15 per cent. Pickins, in 1916, reported 81 perfect results and 17 failures in a series of 100 cases. Labat introduced the combined method of caudal block and transsacral anesthesia.

The early methods of application of cocaine for urethral anesthesia were by injection in solution, and this remains the most common method of administration. Randall, in 1923, reported 5 deaths and 25 cases of alarming toxicity due to the use of cocaine in the urethra. There is a wide divergence of opinion on the use of cocaine for urethral anesthesia. Gardner reported the use of cocaine for eighteen years in approximately 50,000 cases without ill effect, and Walther also did not observe serious reaction. Livermore and Crowell reported 3 deaths. Keyes stated that cocaine should never be used in the urethra. At the Mayo Clinic it has been employed for cystoscopic examinations during the last ten years with satisfactory results. Klotz reported 102 deaths from cocaine; in one instance it was administered by instillation. The important question is the dosage and the use of fresh preparations. Stock solutions are said to become toxic as a result of the growth of fungus.

Chute⁵³ found that the use of spinal anesthesia is indicated less often in operations on the kidney than in operations on the lower part of the urinary tract; it is practically only in disease primary in the lower part of the urinary tract that the two kidneys are equally affected through back pressure. In cases of renal disease that require operation and in which inhalation anesthesia is contraindicated, local procaine hydrochloride anesthesia is used. The most definite indication for the use of spinal anesthesia in urology is the necessity for operation in a condition in which both kidneys have been rendered especially susceptible to the irritative action of inhalation anesthesia as a result of

53. Chute, A. L.: *The Use of Spinal Anesthesia in Urology*, J. A. M. A. 96:88 (Jan. 10) 1931.

urinary back pressure or infection, or of a combination of the two. Prostatic obstruction is the condition most often presenting this picture. In this condition Chute most frequently uses spinal anesthesia. Perineal section for tight stricture is another indication for the use of spinal anesthesia because of the back pressure that it often causes. Spinal anesthesia is particularly indicated and desirable in operations for extravasation of urine, because of the back pressure and sepsis that follows.

Spinal anesthesia is contraindicated for nervous or mentally unstable patients or for those who are strongly prejudiced against its use. Chute rarely uses it for young persons.

In 1922 Chute reported 328 cases of prostatectomy in which spinal anesthesia was used. Since then he has used spinal anesthesia in 512 prostatectomies, mostly for the enucleation of the gland by the suprapubic route. A certain number of the glands was removed by the perineal route. In the 512 cases in which spinal anesthesia was used, 88 per cent gave satisfactory, 10 per cent fairly satisfactory, and 2 per cent unsatisfactory results. In 43 cases a little supplementary anesthesia was used. Chute did not have any immediate or remote fatalities that could be attributed to spinal anesthesia in the 1,000 cases in which it was used.

Ewell⁵⁴ stated that the use of a local anesthetic in the urethra is successful to a certain degree; it permits satisfactory cystoscopic examination and other manipulations in some cases. Cocaine is the only drug that will produce satisfactory anesthesia by topical application to the urethra; in Ewell's experience the reactions from its use have been numerous and at times disconcerting. Cystoscopic examinations and all operative procedures through the cystoscope should be made as painless as possible in order to secure better cooperation from both the patient and the physician. Caudal anesthesia produces sufficient relaxation of the bladder for complete cystoscopic examination and treatment in all types of cases. The operative procedures are painless, and the work of the operator is facilitated. It also provides safe and reliable anesthesia for perineal operations and operations on the external genitalia of men, and operations on the rectum and perineum of women. Intradural caudal anesthesia is recommended because of its simplicity and reliability; complete sacral block anesthesia can be produced by a single intradural injection, whereas by the extradural technic the introduction of a needle and anesthetic solution into the sacral canal and into several or all of the eight sacral foramina would be necessary.

54. Ewell, G. H.: Intradural Caudal Anesthesia in Urology, *J. A. M. A.* **96**: 91 (Jan. 10) 1931.

Because of the advantage of relaxation, intradural caudal anesthesia is of special value for prostatic punch operations.

Lundy⁵⁵ expressed the belief that sacral block anesthesia is safer than spinal anesthesia. The latter gives a greater degree of anesthesia in operations on the bladder for tumor or for diverticula than does sacral or abdominal block anesthesia, but for prostatectomy in patients who are elderly, especially if they are more than 70 years of age, sacral and abdominal block should be employed; debility is a contraindication for spinal anesthesia. It is Lundy's opinion that the technic for using crystals of procaine hydrochloride in spinal fluid is proper, and he is not satisfied with the use of lighter and inferior solutions. Ephedrine is of value in supporting the blood pressure in certain cases. Hypotonus is a definite contraindication to the use of spinal anesthesia.

Campbell⁵⁶ stated that in 1920, at Bellevue Hospital, spinal anesthesia was used in 5 cases; for the last five years it has been the routine method for all urologic operations, except when contraindicated. Spinal anesthesia has been used in about 3,000 of their urologic operations. In only 4 cases was the cause of death attributed to the spinal anesthetic. One man died eight hours after prostatectomy.

It is the practice at Bellevue Hospital to use ephedrine, allowing about twenty minutes before lumbar paracentesis puncture is made. Campbell expressed the belief that barbitol hypnotics are preferable to morphine before operation. If the anesthetic is adequate pharmacologically, there is no indication for morphine and the administration of 1 grain (0.06 Gm.) of phenobarbital preoperatively will not only quiet the patient's nerves but afford the barbiturate counteraction against possible procaine poisoning. Crystals of procaine hydrochloride dissolved in spinal fluid are used; this preparation has produced satisfactory anesthesia in all types of urologic operations.

UROGRAPHY

Cumming⁵⁷ stated that a combined method of fluoroscopy and urography with the Cinex camera has given much satisfaction, with interpretations of increasing value. The securing of a complete, accurately timed series of films, showing the pelvis and ureter in all stages of emptying, will aid greatly in the making of an accurate diagnosis. Actual photographs of the phases of pelvic and ureteral activity promise a

55. Lundy, J. S.: Discussion of Papers by Bumpus, Chute and Ewell on Spinal and Sacral Anesthesia, *J. A. M. A.* **96**:94 (Jan. 10) 1931.

56. Campbell, M. F.: Discussion of Papers by Bumpus, Chute and Ewell on Anesthesia, *J. A. M. A.* **96**:94 (Jan. 10) 1931.

57. Cumming, R. E.: Urography: The Development of a New Method with Physiological Data, *J. Urol.* **24**:587 (Dec.) 1930.

more valuable basis than fluoroscopy for the establishment of accuracy in the interpretation of urograms.

Wesson⁵⁸ stated that for ten years he has made double pyelograms as a routine procedure, using gravity pressure, and has not had any unusual reactions. The unpopularity of double pyelography has been due to attributing to it the effects of surgical shock brought on by urethral instrumentation. Any patient who will tolerate bilateral ureteral catheterization is a subject for double pyelography, since lavage with 1 per cent silver nitrate is more irritating than with 13.5 per cent sodium iodide.

Wesson's simple apparatus for pyelography consists of an 18 inch (45 cm.) ring stand, a double buret clamp, two 25 cc. burets, 80 inches (203 cm.) of one-eighth inch (0.3 cm.) rubber tubing, two adapters and pinchcocks. The head of the table is lowered; when the column in the buret becomes stationary, the pelvis of the kidney is filled. Since only 18 inches of pressure is permitted by the apparatus, which is placed on a low stand, there should be no overinjection, and the patient should not experience pain.

Shapiro and Veseen⁵⁹ stated that with the more common use of nontoxic solutions for pyelography, there is much discussion as to whether it should be used on both sides at the same time. Among the advantages of bilateral pyelography are the time and expense saved the patient by completing the procedure at one examination. Shapiro and Veseen stated that there are also decided disadvantages, and reported 5 deaths following and directly attributable to bilateral pyelography. In 2 cases thorium nitrate was used as the pyelographic medium; in 1 case, 25 per cent sodium bromide, and in the other 2 cases, 12.5 per cent sodium iodide.

Substances that are toxic when absorbed should be distinguished from those that are not, and in making a pyelogram a solution should not be used that cannot be injected, without injury, intravenously in the same quantities and concentrations. The former opinion, that forcing the pyelographic fluid into the straight tubules was the danger in pyelography is not now believed to be the case, except when great force is used. The highest mortality and the most severe reactions seen when colloidal silver was used were in the cases in which there was evidence of systemic poisoning; hemorrhagic diathesis was common, and necropsy showed the presence of colloidal silver in distant viscera as well as in the opposite kidney. Thorium nitrate in 15 per

58. Wesson, M. B.: Interpretation of Pyelograms, *J. Urol.* **24**:595 (Dec.) 1930.

59. Shapiro, I. J., and Veseen, L. L.: Untoward Results in Bilateral Pyelography, *J. Urol.* **24**:621 (Dec.) 1930.

cent solution was next to come into favor. It casts a satisfactory shadow on the roentgenogram, and Burns found that it was only slightly toxic in experimental work. Weld, in his experimental work, found that sodium bromide had a low degree of toxicity when used either intravenously or in the pelvis of the kidney, and the 25 per cent solution cast a satisfactory shadow on the roentgen plate. Graves and Davidoff, in further experimental work with the bromide solution, found that it produced edema of the bladder and partial retention of urine in rabbits. Thrombosis of the small vessels with numerous small hemorrhages was also seen. They ascribed this irritating effect to the fact that sodium bromide in 25 per cent solution is hypertonic as compared with normal body fluids. Physiologic sodium bromide did not produce this condition. Cameron was the first to advocate the use of sodium and potassium iodide for pyelography, but because of its great toxicity it has been discontinued. He first used these salts in 17.5 per cent solution, but strengths as low as 10 per cent have been found satisfactory. Sodium iodide is isotonic in a strength of 14.56 per cent and does not injure the mucosa of the bladder or kidney.

In a case in which infection followed pyelography, the iodide solution lowered the resistance of the tissues, and gave the infection free rein. The pelvic and peripelvic blood vessels must have been the medium of transmission of the infection in order to give rise to abscesses situated solely in the kidney and perinephritic tissues.

Intravenous Pyelography.—Teposu and Jiànù⁶⁰ have used iopax for intravenous pyelography since April, 1930, with satisfactory results. Five cases in which the method was of particular value were described and illustrated with roentgenograms. One case showed symptoms of tetany during the second part of the injection, which lasted for a period of about ten minutes. Following the intravenous injection of calcium the condition returned to normal. It is the contention of the authors that since this patient normally presented hypocalcemia, there was latent tetany which was activated by the injection.

Pyeloscopy.—Hryntschak⁶¹ stated that pyeloscopy is used in all of his cases in which a roentgen examination of the renal pelvis is indicated, but he did not consider applying it as the sole method of examining the filled renal pelvis. Pyeloscopy supplements pyelography in control of the filling process and in observation of the emptying process. By its use it is possible to ascertain whether the tip of the catheter is in proper position in the renal pelvis, whether it has been advanced

60. Teposu, E., and Jiànù, S.: *Intravenous Pyelography*, Cluj. med. **11**:235 (May) 1930.

61. Hryntschak, T.: *Combined Pyeloscopy; Its Clinical Value and Its Technique*, J. Urol. **24**:549 (Dec.) 1930.

too far in a calix or whether it has slipped down into the ureter. By direct observation during the injection, the proper quantity of fluid can be controlled, without relying on the statement of the patient. The statement of the patient regarding an approaching sense of tension frequently does not indicate the crucial moment. With pyeloscopy, the functioning of the organ in its various phases of physiologic activity can be observed.

After introducing the catheter a plain plate is taken. Then the Bucky diaphragm is removed or the patient is transferred to the roentgen table, and the tube under the table is turned on. It is important to outline the catheter clearly and to make certain of the situation of its tip. With the excursion of the diaphragm a movement of the tip of the catheter should be seen. A solution of umbrenal or of 30 per cent sodium iodide is then slowly injected, after which it is possible to ascertain accurately whether the tip of the catheter is in the proper position in the renal pelvis. If the tip is too high, only one of the calices fills. The catheter must then be withdrawn accordingly. When the renal pelvis and calices are sufficiently filled, the injection is stopped. The syringe is attached to the left ureteral catheter in order to prevent any back flow. Careful examination of the filled renal pelvis is made to determine whether all of the calices are properly filled and whether the outlines of the pelvis and calices are sharply defined. This is the proper time to establish the relative position of the renal pelvis in respect to shadows which may have been found in the plain plate, and in regard to palpable tumors in the region of the kidneys. Direct palpation of the tumor, displacement of the kidney by the palpating hand and change of the patient's position will be found useful. After a careful study of the outlines of the pelvis, the first pyelogram is taken immediately. It is important to do this in the postero-anterior direction, as that method fixes what has been seen and makes it available for future detailed analysis. Without further injection of any fluid the ureteral catheter is slowly withdrawn. The onset of peristalsis of the ureter may easily be seen even when the catheter is still in position. The shadow of the renal pelvis then enlarges to include the upper 1 to 2.5 cm. of the ureter. The lower end of the shadow in the upper part of the ureter gradually converges to a point. At the ureteropelvic juncture contraction takes place, which forces the opaque medium in the conus down into the bladder. The formation of the conus should be considered as the normal type of initial peristalsis of the ureter. In observing the emptying of the renal pelvis it is important to note the total time consumed in the process. It is known that a normal renal pelvis ejects about 1 cc. a minute. The time required for complete emptying of the pelvis can be readily estimated from the quantity of fluid injected.

Hryntschak stated the belief that a thorough acquaintance with the screen technic of examining the renal pelvis will, in the future, be a tremendous aid in intravenous pyelography. When proper blending of these two methods has been attained, there will be available the most appropriate and informative means of investigating the anatomy and physiology of the kidneys and ureters.

DISEASE OF THE URINARY TRACT IN INFANTS

Kretschmer⁶² stated that in disease of the urinary tract in infants and children the history of disturbances in the gastro-intestinal tract is of great importance, especially in cases of so-called relapsing pyelitis. Mere pelvic lavage without treatment of any gastro-intestinal lesions is not a progressive method of clearing up a renal infection. Instrumental examination should not be undertaken until there has been a careful study of the urine, preferably daily, roentgenologic examination of the urinary tract and estimation of residual urine, which should be carried out in every case in which there is a suprapubic tumor. The rule should be to study the renal function carefully before subjecting the patient to cystoscopic examination, ureteral catheterization and pyelography.

Malignant tumors of the kidney in infancy and childhood are rare. Tumors of the kidney may be classified as to point of origin as those arising in the renal capsule itself, which are rare, those of the renal pelvis, which are rare when compared with tumors of the parenchyma, and those of the renal parenchyma, which are the common malignant renal tumors. The one constant symptom is the presence of an abdominal tumor. Trauma probably plays a negligible part in the production of these tumors. Gross blood in the urine, which is common in malignant disease in adults, is uncommon in children.

Obstruction to the outflow of urine may occur anywhere along the urinary tract from the urethral orifice to the vesical neck. These lesions result in producing mechanical obstruction. The obstruction may be due to disease of the central nervous system. Fibrosis is the common cause of obstruction at the vesical orifice, although other pathologic changes occasionally are the cause. Diverticula of the bladder in children are generally associated with obstruction at the neck of the bladder. Hypertrophy of the verumontanum may produce marked obstruction to the outflow of urine. Treatment must be directed toward relieving the obstruction. Preliminary drainage of the bladder and improvement of renal function are necessary in some advanced cases. Patients with this type of obstruction have been treated by means of suprapubic

62. Kretschmer, H. L.: Diseases of the Urinary Tract in Infants and Children, Proc. Staff Meet., Mayo Clin. 5:342 (Nov. 26) 1930.

cystostomy with the excision of a wedge-shaped piece from the fibrous neck, followed by digital dilation of the urethra. If valves are present in the posterior urethra, they may be destroyed at the same time.

Chronic renal tuberculosis is rare during infancy and childhood. The diagnosis may be facilitated by careful examination in every case in which pyuria or hematuria is present, as well as in every case in which there are persistent vesical symptoms.

Calculi in the urinary tract of children are relatively rare, and case reports are meager. When stone occurs it is usually found in the bladder. In the average case of renal and ureteral stone the syndrome tallies closely with that presented in cases of stones in adults.

It is generally recognized that the most common disease of the urinary tract in infants and children is what is called pyelitis or cystopyelitis. The pyelo-ureterogram, showing the important rôle of stasis and faulty drainage, and the frequency with which hydronephrosis and stricture of the ureter with dilatation of the ureter occurs, has helped to change Kretschmer's conception of the old clinical picture of so-called pyelitis. In this group of cases the colon bacillus is the common, but not the only, invading organism. These cases are divided into two groups: one in which the disease apparently runs a self-limited course and the patients recover with or without medical treatment and another in which there is a history of several or many recurring attacks of acute pyelitis with its symptoms of chills, fever, sweats and often great prostration. Gastro-intestinal symptoms occur occasionally. When the acute attack subsides the urine seldom clears up entirely, but should it be clear, colon bacilli are sometimes found on culture. In acute cases the treatment consists of rest in bed, the use of large quantities of fluid and careful attention to the gastro-intestinal tract. In the relapsing cases treatment depends on the underlying pathologic condition.

INFECTION OF THE URINARY TRACT

Earlam⁶³ stated that staphylococci are common pathogenic organisms in infections of the urinary tract, either producing an uncomplicated infection or complicating any preexisting lesion. Many staphylococci have the property of splitting urea, with the formation of ammonium carbonate. The commonest of these is *Staphylococcus albus*, certain strains of which have strong urea-splitting properties without being pathogenic in the urinary tract. Other staphylococci may be, but less frequently are, the cause of ammoniac fermentation of the urine. The staphylococci that are able to split urea do not show essential differences

63. Earlam, M. S. S.: Urea-Splitting Staphylococci in Urinary Tract Infections, Brit. J. Urol. 2:233 (Sept.) 1930.

from those which do not have this property, with the exception that the former may possess a greater tendency to infect the urinary tract. The possession of urea-splitting properties by the infecting organism becomes of clinical significance when the infection is gross, with strong urea-splitting power, or when residual urine or urinary lithiasis is present. Treatment for infection due to urea-splitting organisms is essentially that for urinary infections in general.

CORRECTION

In the article by Dr. Bernhard Steinberg, "The Cause of Death in Acute Diffuse Peritonitis" (*ARCH. SURG.* 23:145 [July] 1931), the percentage of animals in the last line on page 147 should read 100 instead of 10.

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HISTOLOGIC STUDIES OF THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

II. CHANGES IN THE CHOROID PLEXUS AND EPENDYMA *

CARL W. RAND, M.D.

AND

CYRIL B. COURVILLE, M.D.

LOS ANGELES

As was outlined in a preliminary report by one of us,¹ a frequent observation in cases of fatal injury to the head is edema of the brain, as well as an increase in the amount of fluid in the ventricular system and in the subarachnoid spaces. We will discuss the question of changes in the brain substance in a later contribution. It is well known that in the majority of cases following injury to the head there is an actual increase in the amount of circulating cerebrospinal fluid. This may be demonstrated clinically by lumbar puncture, when it is usual to find an increase both in pressure and in the amount of recoverable fluid. Several questions present themselves: What is the source or sources of this fluid? Why should there be an excess of the fluid following trauma? What part, if any, does this increase of fluid play in the protective reaction of the brain? What is its bearing on the fatal issue in certain cases? What is its significance in the production of many of the late posttraumatic symptoms? Satisfactory answers to these and similar questions have never been given. It is evident that the increased amount of fluid is due to abnormal physiologic processes taking place within the brain. It is a common conception that the main source of cerebrospinal fluid is the choroid plexus. With this in mind we have been led to study the choroid plexus and ependyma histologically in fatal cases following head injury to see if any changes could be demonstrated which would indicate a hyperactivity of these structures.

Probably the first modern scientific explanation of the source of the cerebrospinal fluid dates from Haller² (1757) and Magendie³ (1825), both of whom considered that it was a product of the leptomeninges, probably the pia mater. Faivre⁴ (1853) first described the

* Submitted for publication, Dec. 5, 1930.

1. Rand, C. W.: Histologic Studies of the Brain in Cases of Fatal Head Injury: I. Preliminary Report, read before the Neurological Section of the American Medical Association, June 27, 1930.

2. Haller, A.: *Elementa physiologiae corporis humani*, Lausanne, M. Bousquet & Co., 1757.

3. Magendie, F.: *Recherches sur le liquide cephalorachidien*, Paris, 1825.

4. Faivre, E.: *Des granulations meningiennes*, Thèse de Paris, 1853, no. 142.

glandular structure of the choroid plexus and indicated that its epithelial cells were secretory. Luschka⁵ (1855) described hyalin-like inclusions in the cells and also suggested that this structure was the source of the fluid. Findlay⁶ (1899) made an exhaustive histologic study of the human choroid plexus under both normal and pathologic conditions. He believed that the epithelial covering of the choroid plexus and that of the ependyma were homologous, and he likewise described variation in the size of the individual epithelial cells. The granular nature of the cytoplasm of the cells, as well as the presence of hyaline droplets and vacuoles, was set forth in detail. He stated: "There is a constant change going on in the epithelial cells, and they normally undergo a process of vacuolation and rupture to form the choroid plexus secretion." Pettit and Girard⁷ (1901, 1902), in a study of the choroid plexuses of animals, showed that the secretion was increased by the administration of muscarine, pilocarpine, ether and theobromine. Under such conditions they found that the height of the epithelial cells was practically doubled, and they described a granular basal and a clear apical zone of these cells which they interpreted as indicating increased secretory activity. Loeper⁸ (1904) described pigmented granules and other granules within the vacuoles of the cells in the human plexus. Further histologic details of the epithelial cells in experimental animals, such as the presence of hyaline droplets and granules of fuchsinophilic or basophilic nature, were described by Schläpfer⁹ (1905), Galeotti¹⁰ (1897), Francini¹¹ (1907) and Engel¹²

5. Luschka, H.: *Die Adergeflechte des menschlichen Gehirns*, Berlin, G. Reimer, 1855.

6. Findlay, J. W.: *The Choroid Plexuses of the Lateral Ventricles of the Brain: Their Histology, Normal and Pathological*, Brain **22**:161, 1899.

7. Pettit, A., and Girard, J.: *Processus sécrétoires dans les cellules de revêtement des plexus choroides des ventricules latéraux, consécutifs à l'administration de muscarine et d'éther*, Compt. rend. Soc. de biol. **53**:825 (July 27) 1901; *Sur la morphologie des plexus choroides du système nerveux central*, *ibid.* **54**:698 (June 14) 1902; *Action de quelques substances sur l'épithélium de revêtement des plexus choroides du système nerveux central*, *ibid.* **54**:699 (June 14) 1902.

8. Loeper, M.: *Sur quelques points d'histologie normale et pathologique des plexus chorioïdes de l'homme*, Compt. rend. Soc. de biol. **56**:1010, 1904.

9. Schläpfer, V.: *Ueber den Bau und die Funktion der Epithelzellen des Plexus chorioideus, in Beziehung zur Granulalehre und mit besonderer Berücksichtigung der vitalen Färbungsmethoden*, Ziegler's Beitr. z. allg. Path. u. Anat. **7**:101, 1905.

10. Galeotti, G.: *Studio morfologico e citologico della volta del diencefalo in alcuni vertebrata*, Riv. di pat. nerv. **12**:480, 1897.

11. Francini, M.: *Sulla struttura e la funzione dei plessi coroidei*, Sperimentale, Arch. di biol. **51**:415, 1907.

12. Engel, E. A.: *Ueber die Secretionsercheinungen in den Zellen der Plexus chorioidei des Menschen*, Arch. f. Zellforsch. **2**:191, 1909.

(1909), who for the most part did not consider them secretory. On the contrary, Yoshimura¹³ (1910) expressed the belief that the vacuoles were formed from an accumulation of the smaller granules as a step in the elaboration of cerebrospinal fluid, which is similar to Findlay's conception. Hworostuchin¹⁴ (1911) described epithelial changes in the form of mitochondria which he believed to be associated with the process of secretion of cerebrospinal fluid. Pellizzi¹⁵ (1911) believed that the granules were associated with the process of secretion but in a different manner. They were considered to absorb fluid plasma, gradually increasing in size until they were extruded from the free margin of the cell. Becht¹⁶ (1920), in a critical review, doubted whether the choroid plexus acts as the major source of the fluid, leaving this an open question. Mestrezat¹⁷ (1912) considered that the choroid plexuses form the cerebrospinal fluid by a process of dialysis. In addition to the foregoing histologic evidence, Weed¹⁸ (1922) summed up in a very complete review the pharmacologic, pathologic and embryologic facts supporting the conception of the secretory activity of the plexus.

MATERIAL AND METHODS

Through the interest of Dr. A. F. Wagner of the coroner's department, abundant pathologic material was placed at our disposal. From this we selected sixty-one cases, most of which had been under our clinical observation. In addition, as a basis of comparison, we studied the choroid plexuses of ten persons who died of other conditions not involving the central nervous system. In all these cases, the body had previously been embalmed, so that the morphologic relationships of the plexus and the ventricle were preserved. The portion of the hemisphere containing the wall of the lateral ventricle and the enclosed plexus was delivered to us in a diluted solution of formaldehyde U. S. P. (1:10). Blocks were taken from the body of the lateral ventricle with its adjacent ependymal lining enclosing the glomus of the choroid plexus. Portions of the caudate nucleus, the thalamus and the overlying corpus callosum were included. These blocks were embedded in paraffin and stained by routine methods, hematoxylin and eosin stain being utilized as a standard for the study of the morphologic aspects of the plexus and the adjacent brain. Suitable sections were also studied with Herxheimer's method for fat, van Gieson's method for connective tissue and hyalin, and the Prussian blue method for iron. Normal and pathologic materials were treated in an identical manner.

13. Yoshimura, K.: Das histochemische Verhalten des menschlichen Plexus chorioideus, *Arch. a. d. neurol. Inst. a. d. Wien. Univ.* **18**:1, 1910.

14. Hworostuchin, W.: Zur Frage über den Bau des Plexus chorioideus, *Arch. f. mikr. Anat.* **77**:232, 1911.

15. Pellizzi, B.: Experimentelle histologische Untersuchungen über die Plexus chorioidei (Adergeflechte), *Folia neuro-biol., Leipzig* **5**:305, 1911.

16. Becht, F. C.: Studies on Cerebrospinal Fluid, *Am. J. Physiol.* **51**:1, 1920.

17. Mestrezat, W.: *Le liquide céphalorachidien*, Paris, A. Maloine, 1912.

18. Weed, L. H.: The Cerebrospinal Fluid, *Physiol. Rev.* **2**:171 (April) 1922.

CASE REPORTS

CASE 1.—*Diffuse subdural hemorrhage; death in four hours.*

A man, aged 55, was admitted to the Los Angeles General Hospital on Dec. 5, 1927, in an unconscious state, having been struck by an automobile a short time before. There was a large hematoma in the right side of the scalp. The right pupil was larger than the left. There was bleeding from the right ear and signs of a pathologic condition in the chest. He died about four hours after the injury.

The coroner's examination disclosed a laceration of the scalp in the right temporal region. There were abrasions and contusions of the face and both eyes were contused. A slight diffuse subdural hemorrhage was found, but no fracture of the skull. The first three ribs on the right side were broken, the lung was lacerated and the pleural cavity filled with blood. The cause of death was given as concussion of the brain with fracture of the ribs and laceration of the right lung.

Histologic Examination.—Choroid Plexus: There was an extensive diffuse edema of the stroma, showing localized collections of fluid. In some areas there was marked pigmentation of the stroma and choroidal epithelium (fig. 12). The pigment granules in the stroma were chiefly within large phagocytic cells, while those in the epithelium were largely in the vacuoles. In some areas of the stroma extensive extravasations of red blood cells and polymorphonuclear leukocytes were found. The blood vessels were empty and showed moderate distention. Numerous so-called "fibrin thrombi" were found within the vessels. Occasional psammoma bodies were present. The epithelial margins were irregular and torn in many places. The epithelial cells were marked by the presence of numerous vacuoles (64 per cent), some of which were extremely large (figs. 4 and 5). The basement membrane for the most part was intact. Masses of coagulated substance were found between the epithelial tufts. The average height of the epithelial cells was 20.39 microns.

Ependyma: There was practically no subependymal accumulation of fluid. Only a minor degree of ependymal vacuolization was present.

Comment.—This case showed the "full blown" type of choroidal changes, i. e., extensive edema of the stroma, increased pigment and red blood cells in the stroma, increased vacuolization (64 per cent) of the choroidal epithelium and an increase in the height of the choroidal cells (20.39 microns). Changes of this sort are often to be seen when death occurs from two to five hours after injury. There was a relatively small subependymal collection of fluid and only a minor degree of vacuolization of this membrane. This picture, which represents the most marked change in the plexus following an injury to the head, was found in five of our cases.

CASE 2.—*Extensive, depressed comminuted fracture of the right parietal and temporal bones; death in four days.*

A colored boy, aged 8, was admitted to the Los Angeles General Hospital at 4 p. m. on Dec. 10, 1927, in an unconscious condition, having been struck by an automobile. There was an extensive depressed fracture on the right side of the cranium. The right pupil was larger than the left; the left arm was rigid and deep reflexes on the left side were exaggerated. The spinal fluid was very bloody. Spastic and occasional jacksonian twitchings on the left side were observed. The

Roentgenograms of the skull showed an extensive fracture of the skull, extending from 1 inch (2.5 cm.) above the external superior margin of the left orbit irregularly and transversely across the frontal bone into the right parietal region, associated with a stellate fracture in the right parietal region with depression. The patient never regained consciousness; he remained spastic on the left side and had occasional left-sided convulsive seizures. He died at 5:30 a. m. on December 14.

The coroner's observations were as follows: There were multiple contusions of the scalp and an extensive depressed fracture of the right parietal and squamosal bones. The fracture extended forward into the frontal bone, thence downward and toward the left across the floors of both anterior fossae of the skull. The cause of death was given as comminuted fracture of the vault and base of the skull.

Histologic Examination.—Choroid Plexus: There was practically no edema of the stroma; the blood vessels were small and empty. A small amount of pigment was found chiefly within the epithelial cells. The free epithelial margin was regular, showing only localized tendencies to distortion. The vacuoles were small and circumscribed and were present in 34 per cent of the cells; the average height was 15.98 microns.

Ependyma: There was practically no subependymal accumulation of fluid and only a minor degree of vacuolization.

Comment.—It is difficult to explain why there were so few changes in the choroid plexus or ependyma. The patient had all the signs and clinical symptoms of severe edema of the brain, yet at death the choroid plexus was little changed. It is possible that the choroid plexus passed through a stage of hyperemia which was subsiding at the time of death. It is also possible that the local injury was more prominent than general changes in pressure, which in comparison were of minor degree.

CASE 3.—*Basal fracture of the skull and subdural hemorrhage on the left side; death in ten hours.*

A Mexican, aged 37, was admitted to the Los Angeles General Hospital on July 5, 1929, in an unconscious condition, having been struck by a street car. A swelling on the left side of the head was noticed. The left pupil was dilated and fixed. The spinal fluid was very bloody. The patient was evidently in shock from which he never recovered. He died at 6 p. m. on the day of admittance to the hospital.

The coroner's examination showed multiple contusions of the head and face; a profuse subdural hemorrhage was found over the left side of the brain, associated with a fracture passing through the left middle and posterior fossae. The cause of death was given as fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was a moderate degree of edema of the stroma, with accumulations of fluid here and there in the larger tufts (fig. 11). The blood vessels were tremendously dilated and a few small thrombi were observed. The epithelial margins were rather irregular, although not extensively torn. Numerous large vacuoles, some of which were seen breaking through the cells, were found throughout the epithelial covering. Sixty-seven per cent of the cells were vacuolated (fig. 3). There was a small amount of pigment in the vacuoles. Many of the nuclei also showed vacuolization and in some instances the nuclei were enclosed in vacuoles (fig. 8B). The average height of the cells was 20.34 microns. The basement membrane was torn in many places.

Ependyma: There was a moderate accumulation of fluid in the subependymal tissue. Localized areas of extensive vacuolization of the ependyma were observed, which in some places was almost detached from the underlying tissue.

Comment.—Marked change in the choroid plexus was present about ten hours after death; the blood vessels were tremendously dilated and there were marked edema of the stroma and vacuolization of the choroidal epithelium. The choroid cells were markedly increased in height (20.34 microns). The ependymal and subependymal changes were less marked than those of the choroid plexus.

CASE 4.—*Hemorrhage of the cerebrum and cerebellum; extensive body injuries; death within two hours.*

A woman, aged 70, was admitted to the Emergency Hospital at 7:35 p. m. on Aug. 10, 1929, having been struck by an automobile. She was moribund on admission and there were evidences of extensive internal injuries to the chest and abdomen associated with fractures of the left leg and the right arm. She never regained consciousness, and died two hours following the injury.

On the coroner's examination the skull was not found to be fractured, but there was slight diffuse hemorrhage over various parts of the cerebrum and extensive hemorrhage covering the cerebellum. In addition to the intracranial condition, there were multiple contusions and abrasions of the body and extremities with fracture of the right humerus and the left tibia and fibula. There were many fractured ribs associated with a rupture of the diaphragm, liver and spleen with intraperitoneal hemorrhage. The cause of death was given as crushing injuries of the chest with concussion of the brain.

Histologic Examination.—**Choroid Plexus:** There was fairly extensive edema of the stroma with some tendency to accumulation of fluid in localized collections beneath the epithelium. "Fibrin thrombi" and concretions were numerous. The blood vessels were distended and empty. The epithelial margin was somewhat irregular. The vacuoles were variable in size, some being fairly large and well outlined, others small and found in the distal portions of the cells; 49 per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.25 microns.

Ependyma: There was practically no subependymal collection of fluid. There was moderate vacuolization of the ependymal cells, not more than is found in some normal brains.

Comment.—An increase in the percentage of vacuolization (49 per cent) and in the height of the choroidal epithelium (17.25 microns) together with fairly extensive edema of the stroma is a consistent observation two hours after a severe injury to the head.

CASE 5.—*Multiple basal fractures of the skull; fracture of the ribs, with laceration of the right lung; a fractured pelvis; death within one hour.*

A woman, aged 29, was admitted to the Emergency Hospital at 11:49 p. m., on Aug. 11, 1929, having been injured shortly before when her automobile was struck by an electric train. She died at the time she entered the hospital. There was evidence of crushing injuries to the chest, skull and pelvis.

The coroner's examination showed numerous contusions and abrasions all over the body and head. The base of the skull was fractured in both the frontal and the right middle fossae. There was no definite injury or hemorrhage of the brain. There were many ribs fractured on both sides and in several places. The right lung was lacerated by several of these fractured ribs. The pelvis was fractured in two places, with laceration of the bladder by bone fragments. Both sacro-iliac articulations were torn loose, and there was extensive hemorrhage into all tissues of the surrounding pelvis. The cause of death was given as a fractured skull, a fractured pelvis and other injuries.

Histologic Examination.—Choroid Plexus: A minor degree of edema of the stroma was present, associated with only an occasional localized collection of fluid. The blood vessels were open and empty. The epithelial margins were fairly regular and the cells were only occasionally vacuolated (25 per cent), and in those the vacuoles were small and circumscribed. The average height of the cells was 12.33 microns.

Ependyma: In some situations, particularly about the blood vessels in the subependymal region, there were large collections of fluid. The ependyma was moderately but consistently vacuolated throughout its extent.

Comment.—The choroid plexus was practically normal, as the patient died before demonstrable changes in this structure could occur. It is likely that shock and hemorrhage played the principal rôle in bringing about the death of the patient, possibly altering the circulation in such a way as to prevent extensive vascular changes in the brain.

CASE 6.—*Multiple fractures of the skull with laceration of the frontal lobes and an extensive subdural hemorrhage; death in four days.*

A woman, aged 30, was admitted to the Los Angeles General Hospital at 10:45 p. m. on Aug. 9, 1929, in an unconscious condition and shock. She was bleeding from both ears; a Babinski sign was present on the left side; the knee jerks were absent. There was marked rigidity of the abdomen. Intra-abdominal bleeding was suspected and a blood transfusion was given. She died without regaining consciousness.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. An extensive subdural hemorrhage was found associated with lacerations of the lower half of the left lower frontal lobe of the brain and multiple fractures of the base of the skull. There were no internal injuries. The cause of death was given as fracture of the skull with laceration of the brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was present, although fairly large localized collections of fluid were found. The blood vessels were much distended and empty. Some free blood was observed in the ventricle, apparently outside of the epithelial tufts. In what was evidently the transverse cerebral fissure, from the appearance of adjacent structures, there were several collections of fibrin and leukocytes which suggested an infectious process, i. e., meningitis. The choroidal epithelium showed regular free margins. The cells were moderately vacuolized (31 per cent), the spaces being small and mostly confined to small ringlike clear zones about the nuclei. Finely granular pigment was situated almost entirely within the epithelial cells. Between the choroidal tufts were found small masses of what appeared to be fibrin in which

a few leukocytes were enmeshed. The average height of the cells was 13.84 microns.

Ependyma: There were some localized collections of fluid beneath the ependyma which was uniformly moderately vacuolated throughout its extent.

Comment.—This case showed evidences of inflammation in the choroid plexus, a condition sometimes seen after three or four days even in the absence of clinical or gross pathologic signs of meningitis. Edema of the stroma was only moderate in this case and little increase in vacuolization or height of the cells was found. The ependyma likewise showed little change. Laceration of the brain with subdural hemorrhage may have obscured the changes in the plexus or the changes may have become less prominent after the four day interval under the extensive administration of a hypertonic solution of dextrose.

CASE 7.—Left occipital linear fracture; death in two days.

A woman, aged 18, was admitted to the Los Angeles General Hospital at 12 noon on Aug. 14, 1929, in an unconscious condition, having fallen earlier in the day while hanging up clothes. There was bleeding from the left ear and a laceration of the scalp in the left occipital region. She died at 11:33 p. m. on August 16.

The coroner's examination showed an extensive subdural hemorrhage and extensive pulping of the right frontal lobe of the cerebrum. There was a fracture line in the left occipital and left temporal bone. The cause of death was given as fracture of the skull following a fall.

Histologic Examination.—*Choroid Plexus:* A moderate degree of edema was found in the stroma; in some areas it seemed absent altogether. The blood vessels were dilated and in many of them red blood cells were still present. An occasional intravascular "fibrin" thrombus was noted, but no concretions were found. The epithelial margins were ragged in many places and the distal portion of the cell seemed to be broken up. The vacuoles were not so numerous (36 per cent) as in some cases; they were moderate in size and did not contain pigment. The average height of the cells was 16.37 microns.

Ependyma: There seemed to be no subependymal accumulation of fluid except in a very few localized areas. The ependyma was not vacuolated beyond normal limits.

Comment.—In this instance there was practically no change in the stroma of the choroid plexus, although the vacuolization of the epithelium was considerably increased and the choroidal epithelium definitely elongated. One would expect more marked changes in view of the extensive cerebral damage found at autopsy, unless the energetic treatment with hypertonic dextrose solution had altered the existing conditions.

CASE 8.—Multiple fractures of the skull and lower extremities; gas bacillus infection; death in thirty-six hours.

A boy, aged 12, was struck by an automobile at 7 a. m. on Aug. 15, 1929. He was irrational on admission to the Los Angeles General Hospital. There was evidence of fracture of the skull and compound, comminuted fractures of the left

leg. He developed a *Bacillus welchii* infection in the lacerations of the left leg and died thirty-six hours after the injury.

The coroner's examination revealed a fracture of the floors of both anterior fossae of the skull, associated with a slight subdural hemorrhage diffused over the cerebrum. The lungs were emphysematous and there was a patch of hemorrhagic pleuritis between the lobes of the left lung. There was a deep laceration of the skin and soft tissues of the anterolateral surface of the left leg, which was swollen and discolored, associated with a compound fracture of both bones just above the ankle. A microscopic examination of the inflammatory exudate from the wound showed the presence of a gas bacillus. The cause of death was given as compound, comminuted fracture of the left leg with gas bacillus infection.

Histologic Examination.—Choroid Plexus: There was little distention of the stroma beyond normal limits. The blood vessels were empty and no localized collections of fluid of any magnitude were seen. The epithelial margins were fairly regular, the cells being quite uniform. Vacuoles were not numerous (33 per cent) and were small and circumscribed, many of them being little more than clear zones about the nucleus. In some cases vacuoles were seen between the cells. The basement membrane was intact in most places. The average height of the cells was 16.54 microns.

Ependyma: There was a fairly definite accumulation of fluid beneath the ependyma with fairly extensive vacuolization of its cells throughout.

Comment.—In this instance the ependymal changes both in vacuolization of the lining membrane and in evidence of subependymal tissue were greater than those of the choroid plexus. The latter showed only moderate vacuolization and some increase in the height of the choroidal epithelial cells. The apparent incongruity between the height of the cells and the percentage of vacuolization may be explained by the fact that, at least in our cases, the epithelial cells are normally higher in children than in adults. In this instance, as in cases 29 and 57, a gas bacillus infection caused death. It is possible that this patient might have recovered if the injury to the head had been the only factor involved.

CASE 9.—*Extensive subdural hemorrhage and contusion of the brain; death in two days.*

A man, aged 38, was admitted to the Los Angeles General Hospital at 11:30 p. m. on Aug. 11, 1929, in an unconscious state, with an odor of alcohol on his breath; he had been injured in an automobile accident. Aside from dilatation and fixation of the right pupil, there were no other positive neurologic signs. Roentgenograms of the skull showed a vertical linear fracture in the midoccipital region. He never regained consciousness and died at 3:05 p. m. on August 13.

The coroner's examination showed an extensive subdural hemorrhage associated with an extensive contusion of the lower surface of the right lower frontal lobe. There were fractures of the floor of the antrum and the posterior margin of the foramen magnum. The cause of death was given as fracture of the skull with contusion of the brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was present and was associated with some local accumulations of fluid. The epithelial margins were fairly regular, although in some individual cells small vacuoles

seemed to have broken through the margin, giving it a rather serrated appearance. The vacuoles were fairly small and circumscribed in most cases and some of them contained pigment granules. Some of the nuclei also contained vacuoles. Thirty-four per cent of the cells were vacuolated and their average height was 13.94 microns.

Ependyma: The subependymal accumulation of fluid was not above normal. Vacuolization of the ependyma was not increased.

Comment.—The degree of edema of the choroid plexus and ependyma was only moderate in this case and far less conspicuous than one would expect when injury to the brain and alcoholism were both present. The odor of alcohol may have been misleading in suspecting intoxication. Intensive intravenous treatments with a hypertonic solution of dextrose with an interval of two days may explain the lack of marked change in the plexus.

CASE 10.—*Extensive contusions of the brain with multiple fractures and internal injuries; death within twenty minutes after the fall.*

A man, aged 46, fell six floors down an elevator shaft at 8:10 a. m. on Sept. 23, 1929, sustaining crushing injuries of the head and chest with other body injuries. When the police ambulance arrived, about 8:30 a. m., the patient had died and the body was taken directly to the morgue.

The coroner's examination showed the skull to be extensively shattered and the brain contused and lacerated. All the ribs were found to be broken, each one in many places, with severe lacerations of the lungs. The liver and spleen were badly lacerated and ruptured and both kidneys were severely contused. There was a fracture of both clavicles, the left scapula, the right ileum and the lower end of the right humerus. The cause of death was given as crushing injuries of the head and chest with other injuries.

Histologic Examination.—*Choroid Plexus:* There was fairly extensive and diffuse edema of the stroma but no large accumulations of fluid were present. Pigment was present in the form of fine granules, found largely in the epithelial cells. The blood vessels were moderate in size, open and empty. The epithelial margins were fairly even although in some cells the distal margin was somewhat ragged. The vacuoles were moderate in size and fairly well circumscribed; they frequently contained rather coarse pigment granules. Twenty-six per cent of the cells were vacuolated; their average height was 13.9 microns.

Ependyma: There were no subependymal accumulations of fluid, although in many local areas there were rows of vacuoles which had collected beneath the nuclei, giving them a rather concentric appearance. Along the free margin of the ependyma in some areas, red blood cells could be found either intact or in the process of degeneration. Their presence was evidently due to ventricular hemorrhage (fig. 20).

Comment.—There was practically no increase in vacuolization or in the height of the cells, but fairly extensive edema of the stroma of the choroid plexus. Relatively greater vacuolization of the ependyma as compared with the choroid gives rise to the question whether ependymal changes occur sooner than choroidal changes after injury to the head. One also wonders whether fluid had collected in the stroma of the plexus

and had as yet failed to manifest its presence in the cells. The multiplicity of factors makes the time element a difficult one to evaluate satisfactorily.

CASE 11.—*Extensive subdural hemorrhage and basal fracture of the skull; death in twenty hours.*

A man, aged 24, was admitted to the Los Angeles General Hospital at 10:10 p. m. on Oct. 18, 1929, following an automobile accident. He was unconscious; the left pupil was dilated and fixed; the knee jerk was active on the right side, but absent on the left; a positive Babinski sign was found on the right. The spinal fluid was bloody and under greatly increased pressure. Both arms were spastic, the left more so than the right. He died at 6:15 p. m. on October 19.

The coroner's examination showed extensive subdural and extradural hemorrhage. There was an extensive fracture of the base of the skull, involving the middle fossae. No other injuries were found. The cause of death was given as fracture of the base of the skull with subdural and extradural hemorrhage.

Histologic Examination.—Choroid Plexus: There was a fairly extensive distention of the stroma, particularly in some portions of the plexus where there was much hemorrhagic extravasation. Fibrin and red blood cells were also found in the ventricular space. There were a few so-called "fibrin thrombi" and in one area were seen a group of concentric concretions. Open, not markedly distended blood vessels and small accumulations of fluid could be seen in the stroma. The free margin of the epithelium was smooth for the most part, although individual cells were somewhat ragged. The basement membrane was well preserved throughout, except where it bounded the larger fluid spaces. Vacuoles, while not numerous, were circumscribed and well defined; 25 per cent of the cells were vacuolated. Most of the free pigment was found in the epithelium. The average height of the choroidal epithelium was 15.56 microns.

Ependyma: There were no extensive subependymal accumulations of fluid. The ependyma was moderately and evenly vacuolated throughout its extent (fig. 18).

Comment.—The principal observation in this case was hemorrhage into the stroma of the choroid plexus and ventricular space. Numerous distortions and irregularities of the nuclei of the endothelial cells of the blood vessels were also shown. There was a minor increase in vacuolization and an increase in the height of the choroidal epithelium cells. The ependyma was moderately and evenly vacuolated throughout. Death was evidently brought about by local hemorrhage rather than by extensive edema of the brain.

CASE 12.—*Contusion of the brain and subdural hemorrhage; multiple fractures of the skull and internal injuries; death within an hour.*

A man, aged 28, was dead on admission to the Emergency Hospital at 11:59 p. m. on Oct. 19, 1929, having fallen from the second story of a building. He had apparently sustained multiple fractures of the skull and internal injuries.

The coroner's examination disclosed a severe general subdural hemorrhage associated with contusions of the base of the brain. There were multiple fractures of the skull involving the basal fossae, especially on the right side. The lungs were severely contused. The stomach was full of blood; no odor of alcohol was detected. There was some hemorrhage around the dorsal spine, but no fracture

was found. The cause of death was given as compound fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: There was moderate edema of the stroma which seemed to involve the tufts somewhat irregularly, some being fully distended and others almost normal in appearance. Fluid spaces, often of considerable dimension, were seen here and there in the stroma. Blood vessels were open and occasionally contained red blood cells. In a few areas both within and without the villi small localized hemorrhages were found. Occasional small "fibrin thrombi," but no concretions, were seen. The free margin of the epithelium was quite regular, being broken up only in local areas. Free pigment, occasionally in good-sized masses and moderate in amount, was found within the epithelial cells. The basement membrane was well preserved everywhere. The vacuoles in the epithelium varied considerably in size, a few being larger than normal. Forty per cent of the cells were vacuolated. The average height of the epithelial cells was 16.31 microns.

Ependyma: There was no extensive subependymal accumulation of fluid. The ependyma was markedly vacuolated in some areas.

Comment.—The percentage of vacuolated cells (40 per cent) was rather more than one would expect when the patient survived his injury only a short time. The epithelial cells were also increased somewhat in size (16.31 microns). Edema of the stroma was also fairly extensive. It seems evident that there are numerous factors that influence the activity of the choroid plexus in injury to the head, so that it is difficult to evaluate the observations properly in some cases. In this case it is possible that the activity may have continued for some time post mortem.

CASE 13.—Subdural hemorrhage with fracture of the skull; fractures of the left pubic bone and both bones of the left forearm; death in from two to three hours.

A man, aged 61, was admitted to the Emergency Hospital at 6:41 p. m. on Oct. 19, 1929, in an unconscious condition, having been struck by an automobile shortly before. There was bleeding from the left ear and there were evident fractures of the left forearm and left leg. His condition became worse and he died at 8:45 p. m.

The coroner's examination revealed a fracture of both bones in the lower third of the left forearm. There were numerous severe contusions, abrasions and a long laceration of the outer aspect of the left leg. A severe general subdural hemorrhage was found. There was a large fracture of the skull, about 7 inches (17.8 cm.) long, extending along the base from the front to the rear on the left side, with some small side branches. The roof of the right orbit was splintered. No injuries of organs of the chest or abdomen were found. The left pubic bone was fractured and some hemorrhage had occurred into the surrounding tissues. The cause of death was given as fracture of the base of the skull with subdural hemorrhage and other injuries.

Histologic Examination.—Choroid Plexus: There was extensive edema of the stroma which seemed to be uniform throughout the plexus. Pigment was rather abundant and was confined almost entirely to the large vacuoles which were found in 66 per cent of the epithelial cells (fig. 9). The free margin of the epithelium

was irregular in many places. There was marked variation in the size of the individual cells, some of them being distended with a single large vacuole or several small ones. The basement membrane was frequently irregular, and in some places seemed to be indented by the underlying fluid (fig. 6). Almost all of the cell vacuoles contained irregular crystalline or granular pigment. The average height of the epithelial cells was 17.43 microns. Some cells were as high as 25 microns.

Ependyma: There was a moderate amount of subependymal edema. The ependyma was irregularly vacuolated; some areas had an abundant number while other parts were free from them.

Comment.—In this case there was marked edema of the stroma, with a great increase in vacuolization (66 per cent); the average height of the cells was also increased (17.43 microns). One cell measured 25.8 microns. Changes of this sort are to be expected, as the height of choroidal reaction apparently comes between two and four hours after injury.

CASE 14.—Typical case of interval subdural hemorrhage; death four days later.

A woman, aged 57, fell down four steps at 9 a. m. on Sept. 21, 1929, striking her head on the walk. She regained consciousness in a short time and remained clear until 3 p. m. on September 24. On that day the right pupil began to dilate and it remained dilated until her death. On the same day she went into coma with Cheyne-Stokes' respiration and a slow pulse rate. A diagnosis of subdural hemorrhage on the right side was made and she was brought about 75 miles to Los Angeles by ambulance on September 25. She died within an hour after arriving at the hospital.

The coroner's examination disclosed a large subdural hemorrhage in the right anterior, middle and posterior cranial fossae. The right pleural cavity contained about 1.5 liters of bloody fluid and the lower lobe of the right lung was severely contused and mushy. The cause of death was given as subdural hemorrhage.

Histologic Examination.—**Choroid Plexus:** There was a moderate degree of edema of the stroma which did not involve the plexus evenly. The blood vessels were distended and in some cases still contained red blood cells. Fluid spaces were to be found in some of the larger tufts. Fairly abundant pigment was found almost entirely in the epithelial cells. "Fibrin thrombi" were numerous and were scattered fairly evenly throughout the entire plexus. The epithelial margin was rather uneven, owing largely to the projection of swollen individual cells. Except in locations bordering the fluid spaces, the basement membrane was intact. The vacuoles in the cells were small and well outlined and usually hugged the nucleus; 64 per cent of the cells contained vacuoles. Pigment granules were scattered throughout the epithelial cells. The average height of the cells was 17.76 microns.

Ependyma: There was practically no subependymal accumulation of fluid, although in some places the cells were tremendously distorted and broken by vacuolization.

Comment.—Vacuolization was much increased (64 per cent); the height of the choroidal epithelium was increased (17.76 microns) and the stroma was moderately edematous, indicating increased activity of the plexus. These changes probably would have subsided if the patient

had been operated on opportunely and the subdural clot removed. We believe that such changes are not necessarily inconsistent with life.

CASE 15.—Fracture of the base of the skull; subdural hemorrhage; death about three hours after injury.

A woman, aged 62, fell down a flight of stairs on Oct. 19, 1929. She was taken to the Altadena Hospital where she died about three hours after admission.

The coroner's examination revealed a compound fracture of the base of the skull and severe general subdural hemorrhage, associated with severe lacerations of the brain. The cause of death was given as compound fracture of the base of the skull with laceration of the brain and subdural hemorrhage.

Histologic Examination.—*Choroid Plexus:* There was moderate edema of the terminal tufts of the plexus which seemed to involve them fairly evenly. Pigment was abundant and was confined almost entirely to the epithelial cells. "Fibrin thrombi" were common and several large concentric psammoma bodies were found. In the stroma fairly well circumscribed collections of fluid were found. In some places the fluid seemed to form clear, distinct, small open places in the stroma. The blood vessels were small and empty in most cases. There was marked variation in the height of the individual cells, some of them being very high. The vacuoles also varied considerably in size, some of them reaching such large proportions as practically to fill the cells, while others were small and circumscribed. In places vacuoles were seen within the nuclei (fig. 8A). Many contained pigment granules. Sixty-eight per cent of the cells were vacuolated; their average height was 19.83 microns.

Ependyma: There were minor subependymal accumulations of fluid and in some places the ependyma was much distorted and torn by the accumulation of vacuoles either within or just beneath the cells. In other places the ependyma seemed to be fairly intact and of normal proportions. The nuclei of the ependymal cells was frequently vacuolated. Discrete pigment granules were to be found in the ependymal cells.

Comment.—Again in this case there is a fairly typical picture of "full blown" choroidal changes, the patient dying three hours after injury. The choroidal vacuolization was much increased (68 per cent), the epithelial cells heightened (19.83 microns) and edema general throughout the stroma. The ependyma likewise showed moderate subependymal edema and marked vacuolization of ependymal cells in places.

CASE 16.—Multiple fractures of the skull; subdural hemorrhage; fractured ribs; death within an hour.

A man, aged 36, who had been struck by a truck, was dead when admitted to the Emergency Hospital at 4:53 p. m. on Aug. 23, 1929.

The coroner's examination disclosed multiple lacerations of the face and scalp; two fractures of the vault were found which ran parallel to the midline. Both extended into the frontal fossae on each side of the cribriform plate. There was also a marked subdural hemorrhage and a hemorrhage into the lateral ventricle. The fifth, sixth, seventh and eighth ribs on the left side were fractured in the nipple line. The cause of death was given as fracture of the skull with a subdural hemorrhage.

Histologic Examination.—*Choroid Plexus:* There was moderate edema of the stroma with a few localized collections of fluid. The tissue was marked by

hemorrhagic extravasations both within and without the tissues of the plexus. This probably accounted for the extensive pigmentation which marked the choroidal epithelium in almost every place. Few so-called "fibrin thrombi" were found. The blood vessels were distended and in many cases were filled with red blood cells. The epithelial cells were fairly regular in size and shape, being marked by an abundance of granular pigment in the cytoplasm. The free margins were somewhat irregular. The basement membrane was intact in most places. Vacuoles were not large and did not seem to be as abundant as in some cases of the series (43 per cent). The average height of the choroidal epithelium was 14.33 microns.

Ependyma: The ependymal tissue showed practically no evidence of accumulation of fluid, although in some places vacuolization of ependymal cells was extensive.

Comment.—Vacuolization of the choroid (43 per cent) was rather marked considering the fact that the patient died within an hour after his injury. The average height of the epithelium was not markedly increased. Edema of the stroma was moderate and ependymal changes were inconsequential.

CASE 17.—Basal fracture of the skull with laceration of the brain and subdural hemorrhage; death in eleven days.

A woman, aged 88, was admitted to the Los Angeles General Hospital at 11:14 p. m. on Oct. 10, 1929, in a confused condition, having fallen off the steps of her home shortly before. She was bleeding from the right ear and a contusion of the right parietal region was found. No deep reflexes were obtained. The spinal fluid was bloody and under pressure. Bronchopneumonia developed and the patient died at 6:10 p. m. on October 21.

The coroner's examination disclosed a fracture of the base of the skull with laceration of the brain and a subdural hemorrhage. The left temporal lobe of the brain was severely lacerated. The cause of death was given as fracture of the base of the skull with laceration of the brain and subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which seemed to be rather diffuse for the most part, although some large fluid spaces were seen. There were numerous so-called "fibrin thrombi" and many large concentric calcospheres were observed in the larger portion of the stroma. The free margin of the epithelium showed considerable irregularity owing to marked enlargement of the individual cells some of which reached unusual proportions. Except in the regions of the large fluid spaces, the basement membrane seemed to be fairly well preserved. The vacuoles were large and discrete for the most part and frequently contained pigment. In some cells there were numerous small vacuoles which gave the epithelium a lacelike structure and gave an irregular outline to the cells. Sixty-two per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.16 microns. One free cell measured 26.3 by 17.6 microns.

Ependyma: There was a marked tendency to the accumulation of fluid in the subependymal space, but the ependyma itself showed little tendency to vacuolization.

Comment.—This case showed more extensive edema of the stroma of the choroid plexus than would have been expected after eleven days. Vacuolization was marked (62 per cent), and the average choroidal cell measured 17.16 microns. One free epithelial cell measured 26.3

by 17.6 microns, an enormous enlargement. There was also marked subependymal edema but practically no tendency to vacuolization of the ependymal lining. Could bronchopneumonia have been a factor in the swelling of this choroid plexus?

CASE 18.—Compound, comminuted, depressed fracture of the skull; extensive subdural hemorrhage and laceration of the brain; death approximately nineteen hours after injury.

A man, aged 26, was admitted to the Emergency Hospital at 6:07 p. m. on Oct. 6, 1929, in deep coma, having been struck by a freight train shortly before. There was clinical evidence of a fracture of the base of the skull and multiple lacerations were found on the forehead and face. He died at 2:10 p. m. on October 7.

The coroner's examination disclosed multiple lacerations of the face and scalp and a depressed comminuted fracture of the skull, 1 by 3 inches (2.5 by 7.5 cm.) in size, beginning in the anterior cerebral fossa on the left side and extending up into the left temporoparietal region. In addition, there were many fracture lines in the bones forming the base of the skull. There was extensive extradural and subdural hemorrhage and lacerations of the left frontal lobe of the brain. The cause of death was given as compound, comminuted, depressed fracture of the skull with laceration of brain.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which irregularly involved the terminal tufts of the plexus. Some of these seemed to be almost normal in their structure. The blood vessels were large and open and most of them were empty. There were a few small "fibrin thrombi" but no psammoma bodies. Finely granular pigment was present in a small quantity in the epithelium. A small amount of blood was found in the intervillous spaces. The epithelial margin appeared irregular in some places where the individual cells had become swollen and extended beyond their fellows. The vacuoles varied in size within wide limits, although they were not as numerous as in some cases. In many cases the vacuole was confined to a ringlike zone about the nucleus. Granular pigment was found in some of them. Fifty per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.57 microns.

Ependyma: There was little tendency to subependymal accumulations of fluid. In most places the ependyma was more vacuolated than normal; in other places it showed no vacuoles.

Comment.—There was less edema of the stroma than one would expect. Vacuolization of the choroidal epithelium was marked (50 per cent) and the cells were moderately heightened (15.57 microns). The ependyma showed an unusual amount of vacuolization with little subependymal edema. The comparatively low height of the average epithelial cell was due to the fact that while the cells were more frequently vacuolated, the vacuoles were very small. This would suggest a generalized but feeble reaction to injury.

CASE 19.—Extensive subdural and ventricular hemorrhage and a lacerated brain; death in ten hours.

A woman, aged 60, was admitted to the Los Angeles General Hospital at 8:30 p. m. on Oct. 17, 1929, in an unconscious state, having been hit by an auto-

mobile. The left pupil was dilated and fixed, and Cheyne-Stokes respiration was observed. The blood pressure varied from 210 systolic and 80 diastolic to 90 systolic and 40 diastolic. She died at 3:15 a. m. on October 18.

The coroner's examination showed a hemorrhage into the right upper eyelid, a few minor abrasions of the feet and a severe hemorrhage beneath the scalp. No fracture of the skull was found, but the entire lower half of the frontal and temporal lobes of the brain on the left side were lacerated to an extreme degree, being reduced to a pulpy mass. There was also marked extradural and intraventricular hemorrhage. The cause of death was given as severe laceration of the brain with subdural and intraventricular hemorrhage.

Histologic Examination.—Choroid Plexus: There was a moderate and symmetrical edema of the epithelial tufts. Abundant pigment was found both in the stroma and in the epithelium, explained probably by the hemorrhagic extravasations both within and without the choroid (figs. 13 and 14B). The blood vessels were moderate in size and most of them contained red blood cells. Numerous large "thrombi" and concentric psammoma bodies were scattered throughout the pedicle of the plexus. The epithelium was regular in outline and the cells showed little variability in their height and substance. The basement membrane was well preserved everywhere. The vacuoles of the cells were not large; they were usually discrete and in many cases were obscured by the abundant pigment. Thirty-eight per cent of the cells were vacuolated. The average height of the choroidal epithelium was 18.92 microns.

Ependyma: There was practically no tendency to accumulation of fluid beneath the ependyma which was unusually vacuolated. Some hematogenous pigment was found within the ependymal epithelium.

Comment.—The abundance of pigment was the most striking observation in the choroid plexus and this probably accounted for the small percentage of vacuolated cells, some of the vacuoles being obscured by masses of granular debris. There was considerable hemorrhage present in the stroma, which probably accounts for the presence of pigment.

CASE 20.—*Marked concussion and contusion of the brain with subdural hemorrhage; compound fracture of the right leg; fracture of the pubic bone; internal abdominal hemorrhage; death from three to four hours after injury.*

A woman, aged 60, was admitted to the Emergency Hospital at 5:33 p. m. on Oct. 18, 1929, with a history of having been struck by an automobile. She was unconscious on admission and never regained consciousness. There was a hematoma in the left parietal region. Other injuries were a laceration above the left upper eyelid, fractures of the upper third of the right tibia and fibula, and a compound fracture of the right pubic bone. She died at 9:05 p. m.

The coroner's examination revealed numerous minor contusions, abrasions and lacerations of the head and body. There were compound fractures of the bones in the upper third of the right leg. A large accumulation of blood was found beneath the entire scalp on the top and back of the head. No fracture of the skull or injury to the brain was found, but there was a severe general subdural hemorrhage. There was free blood in the abdomen and a fracture of the right pubic bone was found. The cause of death was given as injury to the head, a subdural hemorrhage and a fractured pelvis.

Histologic Examination.—Choroid Plexus: A moderate, evenly spread edema of the stroma was found which was marked in places by various-sized accumulations

of fluid. The blood vessels were much enlarged, open and almost entirely empty. Even the large pedicle of the plexus showed the marked effect of the edema; in some places it had the resemblance of a net. There were numerous well formed psammoma bodies as well as "fibrin thrombi." Practically no pigment was to be found. The epithelium showed considerable variation in the height of its cells as well as in the regularity of its free margin. The basement membrane was preserved over large fluid spaces, where it was drawn out into a row of flattened cells. The vacuoles varied considerably in size although none were very large; they were present in 34 per cent of the cells. The average height of the choroidal epithelium was 13.36 microns.

Ependyma: There was little accumulation of fluid in the subependymal spaces and only in one somewhat extended area was any degree of vacuolization shown. In this area the nuclei were distorted by the fluid droplets.

Comment.—The edema of the choroid pedicle was greater than that in other parts of stroma. Vacuolization of the choroidal epithelium was not as marked (34 per cent) as would be expected from the severe nature of the injury to the head. There was little increase in the height of the choroidal epithelium (13.36 microns). Ependymal changes were merely suggested. The picture was unquestionably modified by shock and intra-abdominal bleeding.

CASE 21.—*Large extradural clot and fracture of the base of the skull; death in two days.*

A man, aged 21, was admitted to the Los Angeles General Hospital at 12:30 p. m. on Oct. 6, 1929, having been hit on the head by a billiard cue about 9:30 p. m. the previous day. He was deeply comatose, and the left pupil was dilated and fixed. Roentgenograms of the skull showed a linear fracture of the left parietal bone. A left subtemporal decompression was performed at 1:35 a. m. on October 7, and an extradural clot was partially removed. He died at 8:15 p. m. on October 7.

The coroner's examination revealed a small laceration of the scalp in the region of the bregma. A large extradural clot was found which covered the lateral portion of the parietal lobe, measuring $4\frac{1}{2}$ inches (11.4 cm.) in length, 3 inches (7.6 cm.) in width and about 1 inch (2.5 cm.) at its greatest depth. The base of the skull showed minute lines of fracture on the anterior surfaces of the middle portions of both petrosal bones, and there were hemorrhages in both orbits which could be seen through the orbital plates. A decompression operation had been performed and drains inserted. No internal injuries were found. The cause of death was given as basal fracture of the skull with extradural hemorrhage.

Histologic Examination.—*Choroid Plexus:* There was little edema of the stroma; this did not involve the entire plexus, some tufts retaining practically normal aspects. In those which were distended the blood vessels were wide and empty. A few so-called "fibrin thrombi" were seen, but no psammoma bodies were found. No hemorrhage or pigment in any quantity was observed. The epithelial margin was fairly regular in contour, the cells retaining their morphologic characteristic well. The basement membrane seemed to be well preserved in most places. The vacuoles were not abundant and were usually small and well circumscribed. Thirty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 16.68 microns.

Ependyma: No subependymal edema and little vacuolization were found.

Comment.—Neither the choroid plexus nor the ependyma showed much alteration from normal. Vacuolization of the choroidal epithelium was moderately increased (33 per cent) and the choroidal epithelium was a little higher than normal (16.68 microns). The fluid spaces under the choroidal epithelium were rather large in places and pulsion vacuoles were seen pushing into the basement membrane of the choroidal epithelium. In this case it seems likely that local compression by the blood clot rather than general change was responsible for death. Such cases stand in marked contrast to those of severe injury to the head incident to traffic accidents.

CASE 22.—Extensive subdural hemorrhage and laceration of the right temporal lobe; death in five days.

A man, aged 35, was admitted to the Los Angeles General Hospital at 1:15 p. m. on Oct. 13, 1929, having been injured in an automobile collision. He was restless and semiconscious and was unable to swallow. The blood pressure was 95 systolic and 80 diastolic. On two examinations the spinal fluid was found to be very bloody and under great pressure. Roentgenograms demonstrated no fracture of the skull. He died at 3:30 p. m. on October 18.

The coroner's examination revealed a severe general subdural hemorrhage and an occipital extradural hemorrhage. Severe laceration of the lower portion of the right temporal lobe of the brain was also found. There was a fracture line from the right border of the foramen magnum outward, backward and inward for about 2 inches (5 cm.). The cause of death was given as fracture of the base of the skull with laceration of the brain and hemorrhage.

Histologic Examination.—Choroid Plexus: The connective tissue stroma was variably distended; in some places the edema was extensive, while in other places little change was noted. Some of the enlargement of the tufts was due to marked engorgement of the blood vessels and to hemorrhagic extravasation. There was also considerable free blood in the ventricular spaces. There were numerous and various-sized psammoma bodies in the pedicle of the plexus, and numerous so-called "fibrin thrombi" in the distal tufts. There was a moderate amount of pigment throughout the stroma (fig. 14A). The free margin of the epithelium was regular, although here and there individual cells projected. The basement membrane was intact almost everywhere. The vacuoles were not numerous (20 per cent) and for the most part were small and well circumscribed. The average height of the choroidal epithelium was 14.27 microns.

Ependyma: There were patches of vacuolization although most of the cells were normal. There was no subependymal edema.

Comment.—There was considerable but irregularly distributed edema of the stroma with hemorrhagic extravasation into the connective tissue and ventricular spaces. The choroidal epithelium and ependymal lining were practically normal. The patient lived for five days, but showed no evidence of inflammatory reaction in the choroid plexus as has been frequently seen in other instances.

CASE 23.—Fracture of the skull; extensive subdural hemorrhage and laceration of the brain; death in four or five hours.

A man, aged 65, was admitted to the Emergency Hospital at 4:25 p. m. on Sept. 8, 1929, with a history of having been struck by an automobile. He was in deep coma and did not regain consciousness. There were multiple abrasions and contusions about the body. The blood pressure was 62 systolic and 40 diastolic, and the pulse irregular; the patient died at 8:10 p. m. on the day of the injury.

The coroner's examination showed that the petrous portion of the right temporal bone was extensively comminuted, as was the floor of the right middle cerebral fossa. A large fracture line extended from this region upward and backward to the right occipital region, immediately beneath the scalp wound previously described. There was a severe universal subdural hemorrhage and extensive lacerations of the under surfaces of both temporal lobes of the brain. The fourth to the tenth ribs inclusive were found to be fractured in the posterior axillary line. The cause of death was given as compound, comminuted fracture of the skull with laceration of the brain.

Histologic Examination.—Choroid Plexus: A marked, but not symmetrically distributed, edema of the stroma was found. This tended to be diffuse, although in some tufts various-sized collections of free fluid could be made out. The blood vessels were markedly enlarged and in most places were filled with red blood cells. The free epithelial margin showed considerable variation in its regularity, retaining in some places its fairly smooth contour. In other places the distal ends of the epithelial cells were swollen, which gave them an irregular outline. Except in regions overlying the accumulations of free fluid, the basement membrane was intact. The vacuoles varied considerably in size, some being quite large while others appeared as small perinuclear globules or crescents. Twenty-two per cent of the cells were vacuolated. The average height of the choroidal cells was 13.7 microns.

Ependyma: There was a moderate and fairly extensive vacuolization with definite looseness of the subependymal tissue.

Comment.—A marked edema but practically no heightening of the choroidal cells was observed in this instance. One would expect greater change with death occurring from four to five hours after injury. The ependyma showed more extensive vacuolization and edema of the subependymal tissue than did the choroid. The low blood pressure probably indicated a degree of shock. In cases in which the patient is in shock during the short period of life, we have found only minor changes in the choroid.

CASE 24.—*Typical interval extradural hemorrhage on the left side; death approximately two days after injury.*

A boy, aged 14, was admitted to the Methodist Hospital on Sept. 3, 1929, having been knocked down by an automobile two days before and rendered unconscious for a short time. He was taken first to the Emergency Hospital, then to the General Hospital and then home. He was clear and conscious for three hours after being struck. At 2 p. m. on Sept. 2, he had a terrific headache on the left side of the head and within a few minutes he was delirious with pain. He soon became comatose and was taken to the hospital. Roentgenograms of the skull showed a fracture in the left temporoparietal region. About 8 p. m. on September 3 the left pupil became dilated, and general convulsions with extensor rigidities and double ankle clonus appeared. There was a rapid rise in temperature. The

breathing became irregular and the pulse rapid and weak. The patient died at 10:15 p. m.

The coroner's examination revealed a large extradural hemorrhage in the left temporal region. A fracture of the skull was found, the fracture line extending from the foramen ovale in the left middle cerebral fossa, across the floor of the fossa to the side of the skull on the left, thence upward and backward to a point just above and behind the left ear. The cause of death was given as fracture of the skull and extradural hemorrhage.

Histologic Examination.—Choroid Plexus: Moderate, but evenly distributed, edema of the stroma was found, marked by numerous and often by large fluid spaces. A small amount of pigment was found in the epithelium of the plexus. The epithelium was distended with various-sized vacuoles, which reached large proportions in some instances. Practically all of the epithelial cells showed a diffuse edematous change, which gave the cytoplasm a fine lacelike appearance. In many cases the nuclei were also vacuolated. Some of the nuclei also showed a horseshoe-shaped outline and rupture of the nuclear membrane (fig. 7*A* and *B*). Thirty-two per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 16.74 microns.

Ependyma.—There was a marked tendency to subependymal accumulations of fluid and in some localized places the ependyma was distorted and destroyed (fig. 19).

Comment.—This is the only case of extradural, interval hemorrhage in the series. The cells were edematous, but there was only a relatively slight increase of vacuolization and the choroidal epithelium was only moderately heightened. A marked subependymal edema was observed with great destruction of this membrane in places. Here again was a clearcut case of local, rather than general, pressure, and again the changes in the choroid were moderate. The patient would probably have lived had the hemorrhage been removed in time.

CASE 25.—Fracture of the base of the skull with subdural and intraventricular hemorrhage; death in six hours.

A boy, aged 4, was admitted to the Emergency Hospital at 6:15 p. m. on July 22, 1929, having been struck by an automobile a short time previously. He was unconscious and his condition was poor. He was discharged to the Los Angeles General Hospital, where he died about six hours after the injury.

The coroner's examination revealed a deep laceration of the left side of the upper lip and multiple contusions of the head and body. A fracture across the floor of the right middle fossa at the base of the skull was found, with a resultant subdural and ventricular hemorrhage and concussion of the brain. The right lung was also contused. The cause of death was given as fracture of the base of the skull, with concussion of the brain.

Histologic Examination.—Choroid Plexus: The stroma showed a moderate but symmetrically involved edema. Embedded in several large masses of fibrin, both within and without the stroma, were leukocytes and blood pigment. This suggested some degree of inflammatory reaction. There was a small amount of pigment diffusely spread throughout the epithelium. The basement membrane was distorted in many places by droplets of fluid either in the cell or just beneath it. The epithelial margin was extremely irregular, owing in most cases to a

marked distention of the distal portion of the individual cells. The vacuoles showed considerable variation in size and distribution. A few cells were almost completely occupied with large, clear spaces, while others were filled with numerous small irregular droplets. Fifty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cell was 19.35 microns. In many places the cells seemed to be separated by the accumulation of fluid beneath them.

Ependyma: An occasional localized accumulation of subependymal fluid was seen, especially about the blood vessels. The ependyma itself was free from vacuolization.

Comment.—Edema was moderate, but an inflammatory reaction was present throughout the stroma; this showed how early such a reaction could appear, as the patient died within six hours after injury. Vacuolization was marked (54 per cent) and the choroidal epithelium high (19.35 microns). The ependymal changes were slight in comparison with those of the choroid.

CASE 26.—*Compound, comminuted fracture of the skull; subdural hemorrhage and laceration of the brain; death in ten hours.*

A man, aged 38, was admitted to the Los Angeles General Hospital at 7:40 p. m. on July 19, 1929, in semicoma, having been struck by an automobile shortly before. He was in considerable shock. Roentgenograms of the skull showed a comminuted fracture involving the major portion of the left side of the cranium with a stellate fracture in the frontal region and a linear fracture into the parietal area. He died at 4:55 a. m. on July 22.

The coroner's examination showed ecchymosis around both eyes and over the left side of the head, and a laceration 1 inch (2.5 cm.) deep in the center of the forehead. A compound, comminuted fracture involving the left temporal region and the left middle fossa at the base of the skull was also found associated with laceration of brain tissue and subdural hemorrhage. The cause of death was given as fracture of the base of the skull with laceration of the brain.

Histologic Examination.—**Choroid Plexus:** Moderate generalized edema of the stroma was present, with a tendency to a circumscribed accumulation of fluid. The epithelial margin varied in regularity, but in no place did it present marked serration. The basement membrane seemed to be fairly well preserved throughout. The blood vessels were large, open and empty. The vacuoles varied to some extent in size, but some were unusually large. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cell was 16.74 microns.

Ependyma: No change from the normal was observed.

Comment.—One would expect more changes in the choroid plexus in a patient dying in ten hours from the time of injury, particularly when the damage to the brain was so extensive. This is probably accounted for by the energetic treatment with hypertonic dextrose solution during the hours in the hospital.

CASE 27.—*Extensive comminuted fractures of the vault; laceration of the brain; intracranial hemorrhage; death in sixteen hours after injury.*

A man, aged 38, was struck on the left side of the head about 2 p. m. on Aug. 21, 1929, by a block of redwood 18 by 18 inches (45.7 cm.) and was

immediately rendered unconscious. There was bleeding from both ears. The left pupil was dilated and the patient had several generalized convulsions. Roentgenograms of the skull showed an extensive fracture, with ten different fracture lines in the vault and other fracture lines across the orbits and the bridge of the nose. The blood pressure was 140 systolic and 80 diastolic, the pulse rate 80 and respirations 20. He died at 6:10 a. m. on August 22.

The coroner's examination revealed large bruises of the right shoulder and the right side of the head with extensive hemorrhage into tissues behind the eyelids. There were extensive comminuted fractures of the vault and the base of the skull, with marked hemorrhage between the skull and the membranes covering the brain and between the membranes and the brain. There was also marked bruising of both frontal lobes of the brain. The cause of death was given as comminuted fractures of the vault and the base of skull, with contusions of the brain.

Histologic Examination.—Choroid Plexus: A marked generalized edema of the stroma was present together with some accumulations of fluid in the larger tufts. There was a large number of so-called "fibrin thrombi" scattered throughout the section. There was a small amount of pigment which was confined almost entirely to the epithelium. A few collections of red blood cells and of "fibrin masses" were to be found in the intervillous spaces. The epithelial margin varied considerably in regularity, some areas having a smooth contour, some being serrated and others appearing dentate. The basement membrane was distorted in many instances. The cells showed a moderate number of vacuoles, many of which contained granules of pigment. Forty-two per cent of the cells were vacuolated. These vacuoles varied considerably in size. The average height of the choroidal epithelial cells was 14.62 microns.

Ependyma: There was some looseness of the subependymal tissue suggestive of local edema. In some places the ependyma was moderately vacuolated.

Comment.—The degree of edema was the most marked factor in the choroidal changes. In this case the cells were moderately vacuolated (42 per cent) and little heightened (14.62 microns). The patient was twice given 50 cc. of 50 per cent dextrose solution intravenously. In spite of this, the choroid plexus showed marked changes and the gross changes in the brain were also extensive.

*CASE 28.—*Moderate subdural hemorrhage; a crushed chest; internal abdominal injuries; death in about two hours.*

A man, aged 47, was admitted to the Emergency Hospital at 6:53 a. m. on Dec. 18, 1929, having been struck by an automobile shortly before. He was unconscious and remained so until his death at 7:53 a. m. The blood pressure was too low to be determined. There were evidences of multiple fractures of the ribs, internal injury of the chest and general bruising. Shock was pronounced.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. No fracture of the skull was found, but there was moderate subdural hemorrhage at the base of the brain. No gross injury to the brain was found. All the ribs on the right side were found to be fractured in numerous places and the last six ribs on the left side were fractured in their posterior half. The sternum was completely fractured at the level of the third intercostal space. The right lung showed extensive subpleural lacerations. There was considerable retrosternal hemorrhage. There was a large

hematoma of the transverse mesocolon. Both kidneys showed considerable blood in the pelvis, but were otherwise in good condition. The cause of death was given as concussion of the brain and shock following injuries of the head and crushing injuries of the chest with multiple fractures of the ribs.

Histologic Examination.—*Choroid Plexus:* There was a moderate generalized edema of the stroma which involved the connective tissue of the pedicle as well as the distal tufts. In the larger spaces there were various-sized accumulations of fluid. There was a small amount of coarse granular pigment, which was confined largely to the stroma and the intervillous spaces. The epithelial margins showed considerable variation in their regularity. The basement membrane was distorted in many places owing to the local accumulation of fluid. The choroidal epithelium was marked by extensive vacuolization, the spaces varying considerably in size; some were so large as to fill the cytoplasm of the cell almost completely, while in other instances they were small and numerous and gave rise to a lacelike appearance. In the latter instance the free margin of the cell was irregular, probably incident to the rupture of these small vacuoles. A coalescence of two or more moderately sized vacuoles was not uncommon. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 12.17 microns.

Ependyma: There were large localized collections of fluid beneath the ependyma, particularly about the subependymal blood vessels. In some places the ependyma was markedly vacuolated.

Comment.—Considerable generalized edema of the stroma was present in this case. The vacuolization, while not excessive (34 per cent), demonstrated well the presence of multiple vacuoles which were coalesced in a single cell. The average height of the choroidal epithelium was not increased (12.17 microns), probably because the vacuoles were small. There were unusually large localized accumulations of fluid beneath the epithelium. Had shock not been present, it is likely that this case would have shown a "full blown" type of choroidal change.

CASE 29.—*Compound, comminuted depressed fracture of the skull in the right frontal region; fracture of the right femur; gas bacillus infection of the right leg; death in six days.*

A man, aged 41, was admitted to the Santa Fe Hospital on Dec. 12, 1929. On December 10, while working in a gravel pit, he had been rendered unconscious for a few minutes by the explosion of a dynamite charge. He received a compound, comminuted, depressed fracture of the skull in the right frontal region, and a fracture of the right femur. There were lacerations of the lower extremities caused by flying pebbles and sand. When examined on December 13, he was clear and conscious, with no positive neurologic signs. On the night of December 13, he was somewhat irrational; his temperature rose to about 100 F. On the morning of December 14, he appeared clear. Under ether anesthesia, the depressed fracture in the right frontal region was elevated. At the same time a Steinman pin was put through the right femur by Dr. Chaffin, and skeletal traction was brought on the fracture. It was noted at the time that his right leg seemed larger than his left. On December 15, he complained of pain in his leg, but he was mentally clear. On the night of December 15, his temperature rose to 103 F., and the pain in his leg increased. On December 16, it was evident that a gas bacil-

lus infection of the right leg had occurred. Amputation of the right leg was carried out, and a blood transfusion was given. The patient died about 2 p. m.

The coroner's examination revealed what appeared to be a laceration, 3 inches long, in the right frontoparietal region. This had been sutured and there was a gutta-percha drain in place in the upper angle of the wound. The right thigh had been amputated at about the junction of the middle and upper thirds. The appearance of the stump indicated that an emergency amputation of a badly mangled and probably infected leg had been performed. An elliptical, comminuted, depressed fracture of the skull, $1\frac{1}{4}$ inches by $1\frac{3}{4}$ inches (3.1 by 4.4 cm.), was found in the right frontal region immediately under the laceration previously described. No injury to the brain was found but there was a moderate amount of subdural hemorrhage. The second and third ribs on each side were found to be fractured in the midaxillary line. The cause of death was given as shock and hemorrhage following mangling injuries of the right leg and other injuries.

Histologic Examination.—Choroid Plexus: Moderate generalized diffuse edema of the stroma was present. The blood vessels were moderate in size and empty in practically every case. The epithelial margins were somewhat irregular; the basement membrane was intact in most places and was not markedly distorted. The vacuoles of the epithelium varied considerably in size, some being very small and others assuming large proportions. Some cells contained several large vacuoles which almost entirely replaced the cytoplasm. Thirty-six per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 16.14 microns.

Ependyma: Practically no vacuolization or subependymal edema was found.

Comment.—In this instance there was moderate diffuse edema of the stroma as well as increased vacuolization (36 per cent) of the choroidal epithelium. The cells were somewhat heightened (16.14 microns). No vacuolization of the ependyma and no subependymal edema were found. This patient would almost certainly have recovered from the injury to the head alone, as it consisted of a moderately depressed frontal fracture which was elevated. In addition, he had concussion of the brain. His death was due to a gas bacillus infection of the right leg. It is felt that the changes found in the choroid plexus described often occur in various types of injury to the head from which the patient recovers.

CASE 30.—*Moderate subdural hemorrhage; multiple fractures of the ribs, right forearm and left ankle; death in six hours.*

A man, aged 62, was admitted to the Emergency Hospital at 6:40 p. m. on Dec. 16, 1929, having been struck by an electric train at about 6 p. m. He was transferred to another hospital where he died at about 10 p. m. No adequate record of a physical examination was found.

The coroner's examination revealed multiple abrasions and contusions of the head, body and extremities. The right ulna, the first two ribs and last six ribs on the right side and the sixth rib on the left side were fractured. There was also a dislocation of the ninth on the tenth dorsal vertebra, and of the left sacro-iliac articulations. There was slight subdural hemorrhage, but the brain showed no gross evidence of old or recent injury. Severe contusions and hemorrhages into the muscles of the front and right side of the chest were found. The right

lung was severely lacerated and collapsed and the right pleural cavity was filled with blood. There was a dislocation of the ninth on the tenth thoracic vertebra, with free motion between these two vertebrae. The muscular layers of the stomach wall were ruptured for almost the entire length of the anterior wall of the stomach, but the mucosa and peritoneum were still intact. The liver showed some contusions, but no actual rupture was found. There was complete separation of the left sacro-iliac articulation. The cause of death was given as hemorrhage from multiple fractures of the ribs and a lacerated lung, with other severe injuries.

Histologic Examination.—Choroid Plexus: There was extensive edema of the stroma which involved the whole plexus. Numerous large collections of fluid were found. The blood vessels were open but not particularly distended and in a few cases they contained red blood cells. Numerous "fibrin thrombi" and calcospheres were found, the latter being most abundant in the pedicle of the plexus. Coarse granular pigment was found in moderate amounts both within the stroma and in the intervillous spaces. In the stroma were found large phagocytic cells loaded with light brown pigment. The epithelium showed considerable variation in the contour of its free margin. The basement membrane in most places had been either compressed or distorted by the underlying accumulation of fluid. The vacuoles showed considerable variation in size and distribution; some of them were very large but most of them were moderate in size. In a few individual cells the cytoplasm was tremendously swollen; on close inspection it was found to be loaded with minute vacuoles. Under higher magnifications, the connective tissue of the stroma was seen to be separated by the fluid to form a fine meshwork of fibrils. Thirty-five per cent of the cells were vacuolated and the average height of the choroid epithelium was 13.76 microns.

Ependyma: The ependymal lining was symmetrically and moderately vacuolated. There was no subependymal edema.

Comment.—This was an example of extensive edema of the stroma of the choroid plexus. There was also a considerable increase in pigmentation. Vacuolization was not greatly increased (35 per cent) and the choroid epithelium was of about normal height (13.76 microns). The choroid picture should probably be classified as of the "full blown" type. A maximal amount of edema was present, death occurring approximately six hours after injury. The ependyma and subependymal tissue showed relatively little change.

CASE 31.—*Extensive subdural hemorrhage; period of survival after injury not known.*

A man, aged 57, was admitted to the Los Angeles General Hospital, unconscious and in deep shock, having been picked up by an ambulance at the base of the San Gabriel Canyon. No physical examination was made as the patient died five minutes after arrival at the hospital.

In the coroner's examination no fracture of the skull was found. There was an extensive subdural hemorrhage as well as some hemorrhage into the base of the brain. The cause of death was given as subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive and diffuse edema of the stroma was found involving both the pedicle and the distal tufts. There was a tendency toward localized collections of fluid in the stroma. In one area, apparently in the stroma of the pedicle, was found a tremendous number of

macrophages loaded with débris. In the better stained portions of this area the débris had a reddish cast which seemed to be of the nature of blood pigment. There were fairly numerous "fibrin thrombi" in the peripheral tufts, and numbers of well formed concentric psammoma bodies were found throughout the pedicle. The blood vessels were open and many of those in the distal tufts contained red blood cells. The free margin of the choroidal epithelium was regular in contour in most places. The cells were not extensively vacuolated. Those that were present varied in size from small concentric, clear zones about the nucleus, to large, well circumscribed vacuoles filling the major portion of the cell. The basement membrane was somewhat distorted by the edema of the stroma and may have been destroyed in the regions bounding the larger fluid space. Twenty-six per cent of the cells were vacuolated. The average height of the choroidal epithelium was 11.03 microns. There was a little coarse granular pigment, chiefly in the ventricular space.

Ependyma: There were no alterations except for minor vacuolization in some places, which was not beyond the limits of normal. No subependymal edema was present.

Comment.—The exact nature of the injury or the time that elapsed between the injury and death are not known. The changes in the stroma of the choroid plexus, however, were marked. There was extensive edema with many macrophages loaded with débris. This last observation probably indicates destruction of blood and phagocytosis rather than inflammatory changes in the choroid plexus. The observation that the "full blown" type of choroid plexus appears between two and four hours after injury may indicate that this patient died about that long after his injury.

CASE 32.—Basal fracture of the skull with subdural hemorrhage; death within an hour.

A woman, aged 64, was injured about 8:30 p. m. on Jan. 23, 1930, when she was struck by a hit and run driver. She was dead when picked up by the police. The body was taken directly to the coroner.

The coroner's examination revealed multiple extensive contusions about the head, body and extremities and a compound fracture of the bones of the left leg. There were severe comminuted fractures of almost the entire base of the skull, with severe general subdural hemorrhage. Both lungs showed moderate contusions. The cause of death was given as comminuted fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—**Choroid Plexus:** Moderate edema of the connective tissue stroma was present which seemed to involve the plexus asymmetrically. The pedicle seemed to be more involved than the distal tufts, some of which retained almost their normal morphologic appearance. The blood vessels were open and many of them still contained red blood cells. "Fibrin thrombi" were fairly numerous and an occasional small psammoma body was found. The epithelium showed a fairly regular contour, although here and there marked variations in individual cells were noted. The vacuoles varied considerably in size. In some cells they were numerous and small, giving a lacelike appearance to the cytoplasm, while in others they were large and well outlined. Thirty-nine per cent of the cells were vacuolated. The average height of the choroidal epithelium

was 13.98 microns. In many places the basement membrane had been compressed and distorted. No pigment was to be found in the epithelium or stroma.

Ependyma: The ependyma seemed to be free from vacuolization. The subependymal tissue seemed to be somewhat loose and edematous. Along the ventricular margin red blood cells were seen clinging to the outer surface of the epithelium.

Comment.—In this instance death was due primarily to the injury to the patient's head, and it occurred within an hour, possibly within a few minutes, of the time of the accident. Fulminating subdural hemorrhage, multiple fractures of the skull and moderate edema of the stroma were present. For the most part, the vacuoles were small, breaking the cytoplasm of the cells into lacelike strands. Possibly death occurred before extensive large vacuole formation had time to develop.

CASE 33.—*Basal fracture of the skull; general subdural hemorrhage; fracture of both bones of the left leg; fractured ribs and a torn lung; death in two hours.*

A Japanese girl, aged 4 years, was struck by an automobile, at about 3 p. m. on Jan. 13, 1930. She was taken to the Emergency Hospital and was then transferred to the Japanese Hospital. She was badly shocked, having signs of fractured ribs and clavicle and of hemothorax. The left tibia and fibula were broken. She died at 5:30 p. m.

The coroner's examination showed multiple contusions and lacerations of the body and extremities and a compound fracture of both bones of the left leg. A moderately severe general subdural hemorrhage was found, together with a basal skull fracture, $1\frac{1}{4}$ inches long, extending backward from a point near the inner end of the petrous portion of the right temporal bone. The right lung was collapsed and the right pleural cavity contained about a pint of blood. The upper lobe of the right lung was torn almost completely in two. There was a fracture of the first right rib near its sternal end. The cause of death was given as hemothorax from a ruptured lung and other severe injuries.

Histologic Examination.—**Choroid Plexus:** There was moderate edema of the stroma which involved the terminal tufts symmetrically. The edema seemed to be rather diffuse, although some tendency to local collections of fluid could be observed. The blood vessels were open and empty. There were a few "fibrin thrombi" scattered throughout the section, but no psammoma bodies could be seen. The epithelial margin showed considerable variation in regularity, some places being smooth, while others were much distorted and torn. There was likewise an extensive variation in the vacuoles, some of which were large. Twenty-eight per cent of the cells were vacuolated. In many places the cellular edema was manifested by a collection of small droplets, especially near the distal portion of the cell. The rupture of these small droplets into the ventricular space was probably the explanation for the torn appearance of the epithelial margin. The average height of the choroidal epithelium was 12.10 microns. The basement membrane seemed to be considerably distorted and compressed by the fluid in the stroma.

Ependyma: In some places there seemed to be a definite tendency to subependymal collections of fluid and the ependyma was moderately vacuolated; otherwise it showed no change from the normal.

Comment.—In this instance there was fairly marked edema of the stroma, as well as general edema of the choroidal epithelium. Vacuolization took the form of small droplets. Death occurring within two hours may explain why larger vacuoles were not formed and why more cells were not vacuolated. There was also considerable subependymal edema.

CASE 34.—*Basal fracture of the skull; subdural hemorrhage; both legs broken below the knees; death in from four to five hours.*

A man, aged 34, was struck by an automobile on the evening of Jan. 13, 1930. He was taken to the Emergency Hospital, where he died at 11:45 p. m. There were fractures of both legs below the knees and general bruising.

The coroner's examination revealed multiple contusions and lacerations of the face and scalp. Both bones of both legs were broken just below the knees. A severe general subdural hemorrhage was found. There was a fracture of the base of the skull, consisting of two fracture lines, each about 1 inch long, in the floor of the left anterior cerebral fossa. The cause of death was given as fracture of the base of the skull, with subdural hemorrhage and shock following other severe injuries.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which involved the plexus symmetrically. Many of the tufts were torn and distorted, suggesting a loss of solidarity of the connective tissue stroma. The blood vessels of the terminal tufts were moderate in size and still contained red blood cells in many instances. There were occasional "fibrin thrombi" but no concretions were found. The free margin of the epithelium showed consistently an irregular outline, owing largely to swelling of the distal portions of the epithelial cells. The large vacuoles were not as common as in some of the other cases of the series, but the cells seemed to be marked by diffuse edema which filled the cytoplasm in the form of numerous tiny droplets. Twenty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelial cells was 12.04 microns. The basement membrane was almost universally compressed, distorted or torn by the underlying collections of fluid or edematous stroma.

Ependyma: The subependymal tissue was loosely arranged as though filled with fluid, and the overlying epithelial cells were extensively vacuolized with marked distortion of their nuclei.

Comment.—In this instance edema of the choroid plexus stroma and subependymal spaces was moderate. Vacuolization of the choroid epithelium consisted of tiny droplets filling the cytoplasm. Vacuolization of the ependyma was marked, causing great distortion of the nuclei. Shock probably was a large factor in bringing about the patient's death and in all likelihood is the explanation for the absence of more marked changes in the plexus.

CASE 35.—*Basal fracture of the skull and fulminating subdural hemorrhage; death within an hour.*

A boy, aged 9, was struck by an automobile while crossing the street. He immediately became unconscious, and was dead by the time the ambulance reached the Emergency Hospital. No physical examination was recorded.

The coroner's examination revealed a moderate contusion of the right shin, a contused abrasion on the inner side of the left foot and a compound fracture of both bones of the left leg at about the junction of the middle and lower thirds. A severe general subdural hemorrhage was found. There were severe multiple fractures of the base of the skull. Fractures through the foramen magnum, of the first cervical vertebra and of the odontoid process of the second cervical vertebra were seen with partial dislocation of the skull on the atlas. The cause of death was given as fracture of the base of the skull with subdural hemorrhage and fractures of the cervical vertebrae.

Histologic Examination.—Choroid Plexus: Fairly marked and symmetrically disposed edema of the connective tissue stroma was observed. This seemed to be rather diffuse, with a minor tendency to localized collections of fluid. Some coagulated fibrin and red blood cells undergoing decomposition were found in the ventricular space. The blood vessels were open and in some instances contained red blood cells. Under low magnification the epithelial margin in the main appeared regular, but when observed under higher power it showed considerable laceration. The vacuoles were not as abundant as in some cases, and large ones that filled the entire cell were the exception. The cytoplasm manifested its fluid content by the presence of numerous small droplets, which gave the cell a coarsely granular appearance. Thirty per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.86 microns. The basement membrane was frequently irregular and compressed by droplets of fluid in the stroma (fig. 10). In a few circumscribed areas large phagocytic cells containing brown pigment could be found.

Ependyma: There was little tendency toward subependymal collections of fluid, although the epithelium in some areas was markedly vacuolated. In most places it showed no change from the normal.

Comment.—When one considers that the patient was dead within an hour of the time of the injury, one is surprised at the amount of edema found in the stroma of the choroid plexus. Vacuolization of the choroid epithelium had also begun to increase (30 per cent). There was little change in the ependymal or subependymal tissue.

CASE 36.—*Depressed fracture of the skull, subdural hemorrhage and secondary meningitis; death in four days.*

A Japanese, aged 52, was struck by a street car at 10:30 p. m. on Jan. 20, 1930. He sustained a fractured skull together with severe bruises. Meningitis subsequently developed, and he died at 10:05 p. m. on January 24.

The coroner's examination revealed multiple lacerations and contusions of the head, body and extremities. A severely comminuted, depressed fracture was found in the left anterior and middle cerebral fossae, extending up onto the left parietal bone. There were severe contusions of the lower surfaces of the brain, severe general subdural hemorrhage and hemorrhage into the pons; on the surface of the right cerebral hemisphere there was a large area covered by a fibrinopurulent exudate. The cause of death was given as a compound, comminuted, depressed fracture of the base of the skull with contusions of the brain, subdural hemorrhage and secondary meningitis.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma involved the plexus asymmetrically. Many of the distal tufts and localized areas of the pedicle, particularly about the larger vessels, were markedly distended.

Others retained a more nearly normal morphologic appearance. There seemed to be some localized masses of pigment in the region of the larger blood vessels, but this was not the rule. The blood vessels were open and for the most part empty. "Fibrin thrombi" were numerous in the distal tufts and an occasional psammoma body was found in the pedicle. The epithelium showed a marked irregularity of its free margin owing to swelling of the individual cells. The vacuoles were fairly numerous and in many cells reached unusual proportions. Forty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.56 microns. Some of the individual cells were more swollen by a diffuse edema than by circumscribed vacuoles. The basement membrane was indistinct, in some places owing to a diffuse swelling of the subepithelial connective tissue.

Ependyma: There was little tendency to subependymal accumulation of fluid. Throughout the extent of the ependyma the lining cells were practically free from vacuoles.

Comment.—In spite of the fact that the patient died of secondary meningitis, as shown by the coroner's report, study of the choroid plexus revealed no evidence of recent inflammation. Several other instances (cases 6, 40 and 41) showed undoubted signs of infection in the choroid plexus, but grossly no evidence of meningitis was made out. In this instance, vacuolization (47 per cent) was fairly marked, and the choroidal epithelial cells were considerably heightened (15.56 microns). The ependyma and subependymal tissues showed little change.

CASE 37.—*Concussion; compound fracture of the base of the skull; subdural hemorrhage.*

A man, aged 65, was found lying dead in a storm drain in one of the city parks. There was a wound on the head. It was thought that he stumbled into the drain the previous night.

The coroner's examination revealed several large lacerations and contusions about the head and extremities. A slight degree of subdural hemorrhage was found associated with multiple fractures of the base of the skull. The vessels of the brain were sclerotic, and one small vessel at the base on the right side was completely closed by the sclerotic process. A small necrotic area in the posterior portion of the right internal capsule of the brain was evidently of several weeks' standing. The cause of death was given as concussion of the brain and subdural hemorrhage following compound fracture of the base of the skull; contributory factors were cerebral arteriosclerosis and degeneration.

Histologic Examination.—**Choroid Plexus:** A moderate degree of edema was present which did not involve the plexus symmetrically. Some tufts showed little change from normal. There were a few so-called "fibrin thrombi" in the terminal tufts and an occasional psammoma body in the pedicle. There were red blood cells in the ventricular space. The epithelial margin was irregular, owing chiefly to swelling of the distal end of individual cells which gave a sort of dentate appearance to the outline of the villus. The cells seemed to be much elongated and many of them contained large vacuoles. In some the vacuoles were small and maintained a position close to the nucleus. Thirty-nine per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.48 microns. The basement membrane was not always clearly made out because of the collection of fluid in the stroma beneath it. The blood vessels were open and many of them contained red blood cells. No pigment was found in the epithelium.

Ependyma: There was a definite tendency to the subependymal accumulation of fluid and in most places the epithelium was more vacuolated than normal.

Comment.—In this instance the method of injury was obscure. It was also unknown how long after injury the patient died, or how long he had been dead when found. The study of the choroid plexus and ependyma would indicate that this had been some time, probably more than six hours, as there was considerable edema of the stroma.

CASE 38.—*Compound fracture of the base of the skull; a lacerated brain; subdural hemorrhage; death in four hours.*

A man, aged 64, was struck by an automobile while waiting for a street car. He arrived at the Emergency Hospital at 5:01 p. m. on Jan. 23, 1930, and died at 9 p. m.

The coroner's examination revealed multiple lacerations and contusions of the head and extremities. A fracture of the base of the skull with very severe generalized subdural hemorrhage was found. There was also severe laceration of the lower portions of both frontal lobes of the brain and the left half of the cerebellum was almost completely destroyed. The base of the skull was extensively fractured. The third, fourth and fifth left ribs were found to be fractured in the posterior axillary line. The cause of death was given as compound fracture of the base of the skull with lacerations of the brain and subdural hemorrhage.

Histologic Examination.—**Choroid Plexus:** Extensive edema was observed which involved the choroid plexus quite evenly. In many places various-sized fluid spaces were found. Numerous so-called "fibrin thrombi" were found scattered throughout the plexus. The blood vessels were open and in most cases empty; considerable hemorrhage was found in the ventricular space. The free margin of the epithelium appeared irregular in many places, apparently owing to the rupture of many small, distally placed vacuoles. The vacuoles appeared to be of one or two sizes, the first appearing as fairly small, definitely circumscribed spaces, and the others as larger spaces which in some instances filled the cytoplasm. Fifty-one per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.56 microns. A diffuse cellular edema was manifested by numerous clear droplets which filled the cytoplasm of some of the cells. Pigment in finely divided granules was found in some of them. The basement membrane was irregular and torn in many places owing to local accumulations of fluid.

Ependyma: The subependymal tissue in most places was solid except where the ependyma became continuous with the epithelium of the plexus. Here the tissue appeared much looser and the tall ependymal cells were much vacuolated. In one or two other places the ependyma was vacuolated to a slight degree.

Comment.—The patient died approximately four hours after being injured. The choroid plexus showed marked changes. Edema of the stroma was extensive, vacuolization of choroidal epithelium marked (51 per cent) and individual cells considerably heightened (15.56 microns). The choroidal epithelium also appeared edematous. The choroid plexus resembled the "full blown" type which has been consistently seen in cases in which death occurred from two to four hours after injury.

CASE 39.—*Subdural hemorrhage and pneumonia; death in five days.*

A Mexican, aged 60, was brought to the California Lutheran Hospital at 12:40 p. m. on Jan. 20, 1930, in an unconscious condition. He could be aroused enough to talk, but was unable to give any details regarding his injury. He soon became irrational and delirious and died at 1:30 a. m. on January 25.

The coroner's examination showed multiple abrasions, contusions and lacerations about the head, body and extremities. No fracture of the skull was found, but there was a severe general subdural hemorrhage. Both lungs showed extensive consolidation and contusions. The first six ribs on the left side were fractured near their sternal ends and the first three ribs on both sides showed fractures near their vertebral ends with jagged ends protruding into the cavity of the chest. The cause of death was given as subdural hemorrhage following injury to the head, pneumonia following fracture of the ribs and contusions of the lungs.

Histologic Examination.—*Choroid Plexus:* The edema of the plexus stroma was asymmetrical. Some villi, particularly those along the main pedicle, were tremendously swollen, while other more distally placed tufts showed a minor degree of change. The blood vessels were wide and mostly empty. In the base of the pedicle of the plexus there was an extensive hemorrhagic extravasation. A few "fibrin masses" were scattered throughout the field. The epithelial margin was regular, as was the basement membrane in most places. Over various local accumulations of fluid the latter was either torn or compressed. The epithelium showed a moderate degree of vacuolization, the clear spaces being in the form of either intermediate-sized vesicles or tiny droplets. Thirty-five per cent of the cells were vacuolated. In the latter instance a typical lacelike appearance of the cytoplasm was observed. The average height of the choroidal epithelium was 14.62 microns.

Ependyma: The subependymal tissue was somewhat loose in some places, possibly owing to edema, but the epithelium itself showed practically no vacuolization.

Comment.—The choroid plexus showed only moderate changes five days after injury. The edema of the stroma was moderate and asymmetrical. Vacuolization of the choroidal epithelium (35 per cent) was somewhat increased and the cells were somewhat heightened (14.62 microns). No signs of inflammation of the choroid plexus were made out in spite of pneumonia and death five days after injury. This picture may represent a receding condition rather than that present at the height of the cellular activity.

CASE 40.—*Compound, comminuted, depressed fracture of the skull; meningitis; death in nineteen days.*

A man, aged 52, was hit by an automobile while he was crossing the street at about 7:25 p. m. on Dec. 25, 1929. He was taken to the Emergency Hospital, and then to the White Memorial Hospital where he died at 2:25 p. m. on January 12. No detailed examination was recorded.

The coroner's examination revealed multiple contusions and lacerations of the head and extremities. The meninges were found to be somewhat cloudy and the brain was densely adherent at the tip of the left occipital and left frontal lobes to the fracture of the skull. These two areas seemed to have been severely contused and at the time of autopsy were found to be infected and disintegrating. The

cerebellum was covered with thick grayish-yellow pus. There were an extensive fracture of the base of the skull and a depressed fracture of the vault. The lungs were extensively consolidated and were found to be lightly adherent to the chest wall by recent fibrinous adhesions. The fifth, sixth and seventh ribs on the right side were found to be fractured in the anterior axillary line. The cause of death was given as meningitis following compound, comminuted, depressed fracture of the base of the skull and other injuries.

Histologic Examination.—*Choroid Plexus:* There was moderate edema of the stroma which involved the plexus throughout its extent. The blood vessels were open and in many instances filled with red blood cells. Of particular interest was the presence of polymorphonuclear leukocytes in the intervillous spaces of the distal tufts (fig. 16). A few "fibrin thrombi" were found throughout the plexus. The epithelial margin was irregular owing to the breaking up of the cells consequent to edematous change. The epithelial cells contained vacuoles of widely varied size, some being very large and others in the form of tiny droplets. Forty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.48 microns.

Ependyma: The subependymal tissue was rather loose in structure and in one or two places the epithelium was vacuolated.

Comment.—In this case, in which death occurred from meningitis nineteen days after injury, there were evident changes in the choroid plexus. Edema of the stroma was moderate, and vacuolization of the cells was much increased (43 per cent). The choroidal epithelial cells were also heightened (15.48 microns). Inflammatory changes were present in the stroma and along the ependymal margin where many leukocytes were seen. These inflammatory changes, while definite, were not as marked as one would expect in a case of advanced meningitis.

CASE 41.—*Compound, comminuted, depressed fracture of the skull, with laceration of the brain; death in three and a half days.*

A man, aged 27, was injured about 1 a. m. on Jan. 16, 1930, when his automobile crashed into a cement wall. He sustained an extensive depressed fracture in the right frontal region, together with concussion and contusion of the brain, and he was taken to the Sylvan Lodge Hospital in a state of shock. A blood transfusion was carried out. A spinal fluid leak developed from the wound. On January 18, the depressed bone was elevated and bubbles of air came through the frontal sinus. The patient's condition remained critical and he died at 3:10 p. m. on January 19.

The coroner's examination revealed a depressed fracture in the right frontoparietal region associated with severe hemorrhage into the tissues around both eyes. Other lacerations and contusions about the face, neck and extremities were also observed. On opening the head a severe general subdural hemorrhage and severe lacerations of the right frontal lobe of the brain were found. There was an extremely severe, depressed, badly comminuted fracture of the base of the skull involving both the middle and anterior cerebral fossae and the frontal and right parietal bones. The cause of death was given as compound, comminuted, depressed fracture of the base of the skull, with laceration of the brain.

Histologic Examination.—*Choroid Plexus:* Diffuse edema of the stroma was present which involved the plexus symmetrically. The blood vessels were open and in many cases were filled with red blood cells. An occasional "fibrin thrombus"

was seen and numerous psammoma bodies were encountered in the pedicle. In one or two places hemorrhagic extravasations had taken place in the base of the plexus. Coagulated fibrin and large numbers of polymorphonuclear leukocytes indicated septic meningitis (infection) (fig. 15). The epithelial margin seemed to be symmetrical. The cells contained unusually small vacuoles. Thirty per cent of the cells were vacuolated. Many of the cells showed numerous small droplets in their cytoplasm. Higher magnifications revealed an irregularity of their free margin. The average height of the choroidal epithelium was 13.76 microns. The basement membrane was irregular and distorted in many places.

Ependyma: The ependyma and subependymal tissue showed no variation from the normal.

Comment.—This case showed diffuse edema of the stroma which was symmetrical. Large areas of coagulated fibrin containing many polymorphonuclear leukocytes were found, which seemed to indicate infection. The coroner, however, did not find evidence of meningitis. The ependyma showed leukocytes attached to its margin, also indicative of inflammation.

CASE 42.—Concussion of the brain and other severe injuries; death within an hour.

A man, aged 67, fell down an elevator shaft at about 5:30 p. m. on Jan. 25, 1930, sustaining a fractured pelvis, multiple fractured ribs, concussion of the brain and other injuries. He was taken to the Emergency Hospital in extreme shock and died at 7:10 p. m. on the same day.

The coroner's examination showed multiple contusions and lacerations of the head, body and extremities. No fracture of the skull or free hemorrhage was found, but there was severe capillary hemorrhage throughout the brain substance and pons. In addition a left hemothorax, bilateral congestion of the lungs, multiple fractured ribs, rupture of the spleen and fracture of the pelvis were also noted. The cause of death was given as concussion of the brain, shock following injury to the head, fractured ribs, a punctured lung, hemothorax and other severe injuries.

Histologic Examination.—**Choroid Plexus:** There was moderate edema of the stroma which involved the plexus symmetrically. The blood vessels were full and in most cases contained red blood cells. Numerous "fibrin thrombi" and psammoma bodies were found. The epithelial cells showed a fairly regular margin and the basement membrane was intact in most places. The few vacuoles were fairly well circumscribed. Thirty-five per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.39 microns. No pigment was found.

Ependyma: No change of ependyma or subependymal tissues was seen.

Comment.—In this instance edema of the stroma was slight as would be expected when death was sudden and particularly when shock was present. Vacuolization of the choroidal epithelium was more than one would expect (35 per cent) and the height of the epithelial cells was considerably increased (15.39 microns). When one encounters such observations in conditions that seem to counteract any tendency to pressure, there must be a multiplicity of contributing factors.

CASE 43.—*Basal fracture of the skull; extradural hemorrhage with other injuries; death in six days.*

A man, aged 48, was injured at about 3:40 p. m. on Jan. 20, 1930, when he was struck by an automobile. He was transferred from an Emergency Hospital to the Los Angeles General Hospital on January 21. Examination revealed many superficial lacerations, bleeding from the left ear and fractures of the right arm and right leg. Roentgenograms showed fractures of the bones of the right leg, left elbow and left shoulder, but none of the skull. The patient died at 2:45 p. m. on January 26.

The coroner's examination revealed multiple contusions, abrasions and lacerations of the head, body and extremities. A moderate subdural hemorrhage was found over the left cerebral hemisphere and a moderate extradural hemorrhage at the base of the skull on the same side. There were multiple fractures of the base of the skull. The lungs were both massively consolidated. The sixth rib was found to be fractured in the midaxillary line. The cause of death was given as fracture of the base of the skull with extradural and subdural hemorrhage and bronchopneumonia following fracture of the ribs.

Histologic Examination.—*Choroid Plexus:* There was moderate edema of the plexus. The blood vessels were moderate in size and in many cases were filled with red blood cells. "Fibrin thrombi" were numerous. The free margin of the epithelium was regular in most places, although here and there individual cells seemed to be broken up by the rupture of the surface vacuoles. The vacuoles varied considerably in size and position from multiple small droplets to vacuoles that occupied almost the entire wall. Forty-one per cent of the cells were vacuolated. The average height of the choroidal epithelium was 14.36 microns. The basement membrane showed considerable distortion in many places.

Ependyma: The subependymal tissue seemed to be rather loose and in some places the epithelium was extensively vacuolated.

Comment.—Edema of the plexus was only moderate, but vacuolization of the choroidal epithelium was marked (41 per cent). The choroidal cells were moderately heightened (14.36 microns). The subependymal tissue was edematous and the epithelial cells themselves were extensively vacuolated in places. Vacuolization was rather more marked than is usually seen after the first few hours. It may be questionable whether general intracranial bleeding tended to continue the pressure.

CASE 44.—*Dislocation of the first cervical vertebra; contusion of the spinal cord; subdural hemorrhage.*

A woman, aged 42, was struck by an automobile at 10:10 p. m. on Jan. 25, 1930, while crossing the street. She was picked up dead by the police ambulance shortly afterward.

The coroner's examination showed multiple severe contusions and lacerations. There were a fracture of the left humerus and a dislocation of the right knee. A severe general subdural hemorrhage was found, but no fracture of the skull. The first cervical vertebra was dislocated and the spinal cord was contused but not severed. There were multiple fractures of the ribs with laceration of the lungs and blood in the pleural cavities. There were lacerations of the spleen, liver and left kidney with intraperitoneal and retroperitoneal hemorrhage. The cause

of death was given as dislocation of the skull on the vertebral column, with contusion of the spinal cord, subdural hemorrhage and other severe injuries.

Histologic Examination.—Choroid Plexus: Diffuse symmetrical edema of the stroma was found. There were fairly numerous "fibrin thrombi" and concretions in the stroma. The free margin of the epithelium was regular in most places. The vacuoles were moderate in size and fairly well circumscribed. Fifty-one per cent of the cells were vacuolated. The basement membrane showed but minor distortion. The average height of the choroidal epithelium was 15.05 microns. The blood vessels were moderate in size and in many instances contained red blood cells.

Ependyma: No vacuolization was present in the ependyma nor was any subependymal edema found.

Comment.—In spite of the fact that this patient apparently died within a few minutes of the time of injury, there was diffuse symmetrical edema of the stroma with a marked increase of vacuolated cells (51 per cent). The vacuoles, however, were moderate in size and well circumscribed. Several large cells measuring more than 26 microns were found. The average height of the cells was 15.05 microns. No essential change in ependyma or subependymal tissue was seen. The occurrence of fairly marked changes in the plexus in cases of immediate death suggests the possibility of some postmortem activity of the plexus. We see no other way to explain the occurrence.

CASE 45.—*Concussion of the brain; dislocation of the fifth cervical vertebra; death in forty-one hours.*

A man, aged 21, was injured in an automobile accident at 11 p. m. on Jan. 24, 1930, and was brought to the Los Angeles General Hospital on January 25. He was rendered unconscious at the time of injury, but soon recovered consciousness. Clinically he showed signs of cervical injury to the spinal cord. Roentgenograms showed displacement of the fourth cervical vertebra on the fifth, or vice versa. The patient died about 4 p. m. on January 26.

The coroner's examination showed a few small, moderately severe contusions of the right side of the head and face, a small contused abrasion of the back of the right shoulder, and a similar small contusion of the left shin. No fracture of the skull, hemorrhage or injury to the brain was found. By dissecting the soft parts away from the front of the vertebral column the fourth cervical vertebra was found to be dislocated forward on the fifth cervical vertebra. The cause of death was given as dislocation of a cervical vertebra, with injury to the spinal cord.

Histologic Examination.—Choroid Plexus: The plexus showed a moderate degree of edema which was symmetrical in distribution. The blood vessels were empty and not dilated. Numerous small "fibrin thrombi" were found throughout the field. The epithelium showed a fairly regular outline with little alteration in the morphology of its cells. Many of the cells were small, although some of them reached large proportions. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.82 microns.

Ependyma: The subependymal tissue seemed to be rather loose in some places and a moderate degree of vacuolization was present throughout its extent.

Comment.—This case, in which an injury to the cervical cord was the prime cause of death, is included because the patient also sustained

a concussion of the brain, being unconscious for several hours. He probably would have recovered had the concussion been the only injury. There were moderate edema of the stroma and a considerable increase of vacuolization of the choroid (44 per cent). The choroidal epithelium cells were definitely heightened (15.82 microns). Many nonfatal cases of concussion probably have as many changes in the choroid plexus and ependyma as is shown in this instance, for the head injury itself would correspond to the conception of mild concussion. Hypertonic dextrose solution was not given. This perhaps accounted for the comparatively marked evidence in the choroid.

CASE 46.—Concussion of the brain; subdural hemorrhage; a crushed chest; death in three hours.

A man, aged 72, was injured at 6:30 a. m. on Jan. 28, 1930, in an automobile collision, and was taken to the Emergency Hospital where he died about three hours later. He showed signs of internal injuries to the chest and abdomen, as well as a possible fracture of the skull, subdural hemorrhage and marked shock.

The coroner's examination showed multiple lacerations, abrasions and contusions of the head, body and extremities. No fracture of the skull or injury to the brain was found, but there was moderate subdural hemorrhage over the right occipital lobe of the brain. A retrosternal hemorrhage was found. All the ribs on the right side were fractured, each in a number of places; in their posterior portions they were severely splintered and had lacerated the lung severely. The spleen showed a small rupture and the liver several contusions. The cause of death was given as injury to the head with concussion of the brain and subdural hemorrhage, and multiple fractures of the ribs with laceration of the lung.

Histologic Examination.—Choroid Plexus: There was practically no edema of the stroma. The blood vessels were of average size and empty. Little vacuolization of the choroid epithelium was found and the basement membrane was essentially intact. Vacuolization occurred in 28 per cent of the cells, and the average height of the choroidal epithelium cells was 11.18 microns.

Ependyma: The ependyma nearest the choroid plexus was moderately vacuolated.

Comment.—In spite of the fact that an interval of three hours elapsed between injury and death in this case, there were no changes in the choroid plexus or ependyma worthy of mention. The extensive injuries to the lungs, spleen and liver may have accounted for the patient's death, instead of the injury to the brain which may well have been relatively trivial. Furthermore, the age of the patient and shock probably prevented more marked changes.

CASE 47.—Fracture of the skull, with subdural hemorrhage; death in about two weeks.

A man, aged 62, was admitted to the Los Angeles General Hospital on Jan. 27, 1930, with a history of having been struck on the back of the head two weeks previously. Examination showed fracture of the skull and course râles throughout the chest. All the reflexes were increased and a bilateral Babinski sign was present. The patient died on January 28.

The coroner's examination revealed a few discolored areas on the back of the shoulders, arms and thorax, which were superficial. A large subdural hemorrhage covered the posterior half of the right hemisphere of the brain, the blood being thin and fluid. There was a fracture running from the internal occipital protuberance forward into the opening of the spinal canal. The cause of death was given as fracture of the base of the skull with subdural hemorrhage.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which seemed to be diffuse and involved the choroid plexus throughout its extent. The fluid spaces were usually small. "Fibrin thrombi" and psammoma bodies were numerous. The choroid epithelium showed numerous vacuoles, some of which contained pigment; 40 per cent of the cells were vacuolated. The average height of the choroidal epithelium was 16.85 microns. The basement membrane was distorted and compressed in some places. Hemorrhagic extravasation was present in the base of the pedicle.

Ependyma: No subependymal edema or vacuolization of the ependyma was observed.

Comment.—A fairly extensive edema of the choroid stroma was found, together with increased vacuolization (40 per cent) and heightening (16.85 microns) of the epithelial cells. From the fact that such diffuse changes were still present in the choroid two weeks after injury, it is evident that cerebral edema may persist over a period of weeks, especially if untreated. In contrast to this are cases in which energetic treatment with hypertonic dextrose solution was given; these showed minor changes in the choroid, death being brought about by other causes.

CASE 48.—*Basal fracture of the skull; subdural hemorrhage; death in eleven days.*

A man, aged 59, was found lying unconscious on the sidewalk, bleeding from a wound on the left side of the scalp, at about 7 p. m. on Jan. 14, 1930. He soon regained consciousness. Except for periodic twitching of the right side of his face he progressed fairly well until the evening of January 19; then terrific headaches developed and at times the patient became drowsy. He was taken to the California Hospital where the results of neurologic examination were essentially negative. A lumbar puncture revealed a very bloody spinal fluid under 200 mm. of pressure. Roentgenograms of the skull revealed a linear fracture in the left temporal region. On January 22, marked cerebrospinal rhinorrhea developed and the headaches increased. At operation on the evening of January 22 a large amount of bloody spinal fluid was removed and a soft rubber drain was placed under the left temporal lobe. The following morning the cerebrospinal rhinorrhea had stopped. The patient became worse, however, and died on January 25, at 4:55 p. m.

The coroner's examination showed that the vault and base of the skull were fractured on the left side. A decompression had been performed and no hemorrhage was found at the time of autopsy. There were two small distinct areas of contusion of the right middle lobe of the brain. The left eye showed ecchymosis and there was a contusion on the right knee. The cause of death was given as fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: Moderate edema of the stroma was found which seemed to be more marked in some places than in others. Scattered here and there in the intervillous spaces were little groups of leukocytes and fibrin which suggested an inflammatory process. A few "fibrin thrombi" and psammoma bodies were found. The epithelium showed irregularity of its free margin owing largely to the prominence of the individual cells, but in a minor degree also to a breaking up of the distal margins. Many of the cells were vacuolated, containing various-sized, clear spaces, only a few of which reached unusual proportions. Fifty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 14.89 microns. The basement membrane showed moderate changes in its contour. A few leukocytes were found in the edematous stroma.

Ependyma: The ependyma showed vacuolization in some areas, but did not differ widely from the normal in appearance.

Comment.—This case showed areas of inflammatory reaction in the free ventricle shown by leukocytes in its cavity. The vacuolization of the choroidal epithelium was much increased (54 per cent) and a few leukocytes were found in the edematous stroma. In spite of these histologic changes no gross reaction was noted by the coroner. As little evidence of hemorrhage or damage to the brain was found, it is likely that edema played an important part in the clinical picture. To a lesser degree inflammatory changes may have contributed to the patient's death.

CASE 49.—*Subdural and extradural hemorrhage with fracture of the skull and internal injuries; death in thirty-two hours.*

A woman, aged 45, was injured in an automobile collision about 6:50 p. m. on Jan. 13, 1930. She was rendered immediately unconscious and remained so until her death. There were clinical signs of fracture of the skull with a subdural hemorrhage and fracture of the left clavicle, ulna and radius, as well as multiple fractures of the ribs. She died at the Emergency Hospital at 2:27 a. m. on January 15.

The coroner's examination revealed multiple contusions and lacerations of the head, body and extremities. The left clavicle and both bones of the left forearm were broken. A large extradural hemorrhage was found on the left side of the head with severe compression of the entire left cerebral hemisphere; there was severe general subdural hemorrhage and slight contusion of the under surface of the brain. There were extensive comminuted basal fractures of the skull in both posterior cranial fossae, in the left middle fossa and through the cribriform plate. There were multiple fractures of the ribs on the left side associated with laceration of the left lung and hemothorax. The right lung was severely contused and the lower lobe showed an early consolidation with a fibrinopurulent exudate on its surface. The cause of death was given as subdural and extradural hemorrhage following comminuted basal fracture of the skull and other severe injuries.

Histologic Examination.—Choroid Plexus: There was a moderate diffuse edema of the stroma which seemed to involve all portions of the plexus alike. The blood vessels were open and in most cases empty. The pedicle had been filled with fluid so that it presented nearly netlike septums separated by wide fluid spaces. The solid connective tissue masses were studded with psammoma bodies. The

epithelium of the distal tufts was regular. The basement membrane was fairly well preserved. Vacuolization occurred in 37 per cent of the cells. The vacuoles were not markedly increased in number and varied in size within fairly wide limits. The average height of the choroidal epithelium was 13.58 microns.

Ependyma: The subependymal tissue seemed to be fairly solid and the epithelium showed no vacuolization except in a few circumscribed locations.

Comment.—This case showed moderately diffuse edema of the stroma of the choroid plexus as well as increased vacuolization (37 per cent) of the choroidal epithelium which was moderately heightened (13.58 microns). The ependyma and subependymal tissue showed little change. From the coroner's observations it seemed evident that intracranial hemorrhage and shock rather than cerebral edema were the chief factors in bringing about the patient's death.

CASE 50.—*Basal fracture of the skull, subdural hemorrhage and internal injuries; death in one hour.*

A woman, aged 50, was hit by an automobile while crossing the street at about 7:55 p. m. on Jan. 29, 1930. She was taken to the Emergency Hospital, where she was found to have sustained a fracture of the base of the skull, a crushed chest, a fractured pelvis and other internal injuries. She died an hour later.

The coroner's examination revealed severe contusions and abrasions of the head, trunk and extremities as well as a fracture of the left clavicle and pelvis. A severe subdural hemorrhage was found over the entire right cerebral hemisphere, with compression and pushing of the hemisphere toward the opposite side. There was an extensive fracture of the base of the skull on the left side involving the left middle cerebral fossa and the left vault. The second to seventh ribs, inclusive, on the left side of the chest were fractured with hemorrhage into the left pleural cavity. The diaphragm was torn on the left side and the stomach protruded through into the pleural cavity. The cause of death was given as fracture of the base of the skull, with subdural hemorrhage and other severe injuries.

Histologic Examination.—Choroid Plexus: There was marked balloon-like distention of the plexus which involved its entire structure. The blood vessels were not particularly prominent and in most instances were empty. "Fibrin thrombi" were numerous throughout the section. The entire stroma seemed to be broken up by the increase in fluid which was particularly marked in the large pedicle of the plexus. In the ventricular space there was a certain amount of free blood and coagulated fibrin. The free epithelial margin was inclined to be irregular owing both to the enlargement of individual cells and to the rupture of small distal vacuoles. The epithelial cells contained numerous vacuoles, many of which were large and, in some cases, unusual in size. Fifty-six per cent of the cells were vacuolated. The average height of the choroidal epithelium was 17.20 microns. The accumulation of fluid in the space between the blood vessels and the epithelium so distorted the structures in most places that the basement membrane could not be seen clearly.

Ependyma: The ependyma was vacuolated practically throughout its extent, although more marked in some places than others.

Comment.—This case presented "full blown" changes in the choroid plexus. The stroma was ballooned out, vacuolization of cells was high

(56 per cent) and the cells were increased in size (17.20 microns). The ependyma also showed marked vacuolization. The association of these marked changes with extensive intracranial hemorrhage and other severe injuries occurring in such a short period seems unusual.

CASE 51.—Basal fracture of the skull, contusion of the brain and internal injuries; death within one hour.

A man, aged 25, fell from the fifth story of a building at 5:27 p. m. on Feb. 6, 1930. He was taken to the Emergency Hospital where he showed signs of extensive internal injuries as well as fracture of the base of the skull. He died at 6:15 p. m.

The coroner's examination revealed extensive and marked abrasions, contusions and lacerations involving all parts of the body. The left wrist was partially dislocated. A severe subdural hemorrhage was found over the entire right cerebral hemisphere, with severe contusion. An extensive fracture of the base of the skull was found which involved the left middle fossa, the region of the sella turcica and the cribriform plate. The first nine ribs on the left side were fractured near their middle and the left pleural cavity contained about 1 quart (946 cc.) of free blood. Both lungs were lacerated. The cause of death was given as fracture of the base of the skull, with contusions of the brain, subdural hemorrhage and other severe injuries.

Histologic Examination.—*Choroid Plexus:* Rather extensive edema was found which involved the plexus more or less symmetrically. The blood vessels were not particularly distended and most of them were empty. Fluid spaces formed a conspicuous feature. "Fibrin thrombi" were fairly common and there were numerous psammoma bodies in the pedicle of the plexus, some of which had reached a tremendous size. The epithelium showed considerable variation in its reaction to the swelling of the stroma. In some places the cells appeared vacuolated, but for the most part little change from the normal was observed; 28 per cent were vacuolated. The vacuoles were small and well outlined. The average height of the choroidal epithelium was 13.24 microns. The basement membrane was frequently distorted and torn by the underlying fluid.

Ependyma: In some locations there was a definite accumulation of fluid in the subependymal tissues over which the epithelium was tremendously distorted.

Comment.—This case showed extensive edema of the choroid plexus, but only moderate vacuolization and little increase in the height of the cells. The ependyma showed more changes than did the choroid plexus. It may be that edema occurs first in the plexus and is followed by activity of the epithelial cells later, at least under certain conditions.

CASE 52.—Subdural hemorrhage; fractured right femur; death in six days.

A man, aged 89, was struck by a bus at 8:30 a. m. on Feb. 3, 1930. He was sent to the Emergency Hospital and was transferred to the Los Angeles General Hospital where he died at 11:50 p. m. on February 9. The right femur was fractured. Bronchopneumonia developed from which the patient died.

The coroner's examination revealed a fracture through the neck of the right femur with external rotation of the distal fragments. An excess of cerebrospinal fluid was found; over the left cerebral hemisphere the brain and dura were markedly stained by changed blood from an old hemorrhage (one week or ten days). No fracture of the skull was found. The dependent portions of both

lungs were consolidated and friable, presenting the picture of a well consolidated hypostatic pneumonia. The cause of death was given as hypostatic pneumonia following fracture of the right femur.

Histologic Examination.—Choroid Plexus: Rather marked edema of the stroma was present. The blood vessels were dilated and empty. The free margin of the epithelium was slightly irregular owing largely to unequal swelling of the cells. The vacuoles varied in size, although those of unusual proportions were rare. Thirty-seven per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.24 microns. The basement membrane was fairly well preserved.

Ependyma: The subependymal tissue showed little localized evidence of fluid. Vacuolization was present to a marked degree in one locality only.

Comment.—At the end of six days this patient showed marked edema of the stroma and considerable vacuolization (37 per cent). The cells averaged 13.24 microns in height. This patient was the oldest in the series. The choroid plexus did not show inflammatory changes as have frequently been seen several days after injury. The cause of increased vacuolization so long after injury is not clear.

CASE 53.—*Fracture of the skull; subdural hemorrhage; ruptured liver; death in six days.*

A man, aged 63, was injured in an automobile accident at 8:30 a. m. on Feb. 3, 1930, and was admitted to the Los Angeles General Hospital where he died at 12:25 p. m. on February 9.

The coroner's examination revealed a laceration and contusion in the right temporal region, a contusion of the right eye, an abrasion on the right cheek, and contusions on the other side of the right arm and on both knees. A subdural hemorrhage over the base and lateral surface of the left temporal lobe of the brain was found associated with a fracture of the right parietal region and the right anterior and middle fossae. The liver was ruptured in six places, the gallbladder was also ruptured, and all the abdominal viscera were stained with bile. The cause of death was given as fracture of the base of the skull with rupture of the liver and gallbladder.

Histologic Examination.—Choroid Plexus: Rather marked edema of the stroma was found which involved the entire plexus. "Fibrin thrombi" were numerous and occasional psammoma bodies were found in the pedicle. The blood vessels were moderate in size and most of them were empty. The free margin of the epithelium was irregular, owing to marked vacuolization of the cells. Sixty-four per cent of the cells were vacuolated. For the most part, the vacuoles were uniform in size although some were large enough to occupy the larger portion of the cytoplasm. The average height of the choroidal epithelium was 15.99 microns. The basement membrane varied in regularity, although in most places it was definitely distended.

Ependyma: A marked increase in the vacuolization of the ependyma was observed, particularly in the region where it becomes continuous with the epithelium of the choroid plexus. The subependymal tissues showed little alteration.

Comment.—At the end of six days this case showed marked edema of the stroma and high vacuolization of the cells (64 per cent). The choroidal epithelium was heightened (15.99 microns). The changes

here were about as marked as are ever seen in the "full blown" cases in which death occurs in from two to four hours.

CASE 54.—Basal fracture of the skull; subdural hemorrhage and contusion of the brain; death within one hour.

A boy, aged 12, was injured in an automobile collision at 7 p. m. on Feb. 8, 1930, and died before he arrived at the Emergency Hospital.

The coroner's examination revealed severe and extensive superficial injuries of the head, body and extremities. A severe general subdural hemorrhage and a contusion of the right cerebral hemisphere were found. There was an extensive fracture of the base of the skull, involving all the cerebral fossae on the right side and the middle fossa on the left. The cause of death was given as fracture of the base of the skull, with a subdural hemorrhage and a contusion of the brain.

Histologic Examination.—*Choroid Plexus:* There was moderate edema of the entire plexus. A localized hemorrhagic extravasation was seen in one portion of the pedicle associated with pigmentation in the regional cells. No "fibrin thrombi" or calcospheres were present. Viewed under low power magnification, the choroidal epithelium seemed fairly regular, but under higher magnifications the distal portions of the cells were seen to be serrated. Vacuolization of these cells was not extensive, 50 per cent of the cells being so involved. The average height of the choroidal epithelium was 14.27 microns. The basement membrane was fairly well preserved in most places. No pigment was present except in the region of the hemorrhagic extravasation.

Ependyma: Some looseness of the subependymal tissues was found associated with vacuolization which was marked in one or two extensive stretches.

Comment.—In spite of the short time that elapsed from the time of injury until death (less than one hour), this case showed moderate edema of the stroma of the choroid plexus and 50 per cent of the cells were vacuolated. The subependymal tissue was also loose and the epithelial cells considerably vacuolated.

CASE 55.—Concussion of the brain; a ruptured bladder; death in nine days.

A woman, aged 36, was injured in an automobile accident on Jan. 19, 1930, and was unconscious for twenty-four hours. A ruptured bladder was found on abdominal exploration. Roentgenograms revealed multiple fractures of the ribs, a fractured pelvis and pleural effusion on the day of the patient's death, January 28.

The coroner's examination showed multiple contusions of the body and extremities. A large accumulation of blood was found beneath the scalp over the right parietal region. No fracture of the skull, injury to the brain or intracranial hemorrhage was found. All the ribs on the right side as well as two on the left were fractured near their vertebral ends with laceration of both lungs and hemothorax. The left side of the diaphragm was ruptured, and a large portion of the spleen and part of the splenic flexure of the colon protruded through into the left pleural cavity. The bladder showed a recently sutured opening in the front with a self-retaining catheter sutured in place and extending out through the surgical wound in the abdomen. The bladder was contracted and contained a great deal of thick, purulent looking material. The right sacro-iliac articulation was fractured. The cause of death was given as multiple fractured ribs with lacerated lungs, hemothorax and other severe injuries.

Histologic Examination.—Choroid Plexus: A minor degree of edema of the stroma was present and the blood vessels were open and empty, 30 per cent of the cells being vacuolated. The choroidal epithelium was regular; the vacuoles were small. The average height of the choroidal epithelium was 12.38 microns. The basement membrane was fairly well preserved throughout. Occasional "fibrin thrombi" were seen.

Ependyma: No subependymal accumulations of fluid were present. The ependymal lining was vacuolated only to a moderate degree.

Comment.—As would be expected from the coroner's report the injury to the head was relatively minor in comparison with other internal injuries. The choroid plexus showed little change from the normal. It is likely that similar changes occur in many persons with concussion who recover.

CASE 56.—Basal fracture of the skull; laceration of the brain and internal injuries; death within an hour.

A man, aged 25, fell from a building at 9:30 a. m. on Feb. 8, 1930, and was picked up dead by the police ambulance attendants shortly afterward.

The coroner's examination revealed multiple severe contusion, abrasions and lacerations covering the head, body and extremities. There were fractures of the right clavicle, small bones of the right hand and right femur, together with dislocation of both hip joints. Severe contusions and lacerations of various portions of the brain and cerebellum were found, but there was only moderate hemorrhage. There was a severe comminuted fracture of the entire base of the skull. All the ribs on the right side and four on the left side were fractured and a fractured dislocation of the tenth and eleventh dorsal vertebrae was found. Both lungs were lacerated and free blood was present in the pleural cavity. The left side of the diaphragm was ruptured and the spleen and the splenic flexure of the colon protruded into the pleural cavity. The liver and kidneys were torn and there was much free blood in the abdominal cavity. There was a complete fracture of the ileum on each side of the sacrum. The cause of death was given as fracture of the base of the skull with lacerations of the brain and other severe injuries.

Histologic Examination.—Choroid Plexus: Extensive edema of the stroma was found which involved the entire plexus. There were occasional "fibrin thrombi," but no psammoma bodies were seen. The blood vessels were moderate in size and many still retained red blood cells. Various-sized fluid spaces were found scattered throughout the stroma. The free margin of the epithelium was irregular in some places, evidently owing to rupture of tiny vacuoles. The epithelial cells were not markedly vacuolated (30 per cent). The average height of the choroidal epithelium was 12.54 microns. The vacuoles present were small. The basement membrane seemed to be well preserved, except over large accumulations of fluid.

Ependyma: The ependyma everywhere retained its normal morphologic aspects.

Comment.—In spite of the short time elapsing between injury and death, extensive edema of the choroid plexus stroma was evident, but vacuolization of the cells and heightening of the choroidal epithelium were not marked. Probably edema of the stroma begins before vacuolization of the choroidal epithelium appears. This is to be expected if fluid from the stroma passes into the epithelial cells.

CASE 57.—*Subdural and petechial hemorrhages of the brain; gas bacillus infection of the arm; death in nine days.*

A youth, aged 18, went over a cliff in an automobile on Feb. 2, 1930. He fractured the right arm and was in deep coma until February 11, on which day the gas bacillus was found in a culture and the patient died.

The coroner's examination disclosed bruising around the inner corner of the right eye and a compound, comminuted fracture of the right humerus. This fracture was infected and pus exuded from a wound in the arm. There was a fracture of the right femur and a large abrasion of the anterior portion of the thigh. No fracture of the skull was found, but there were the remains of a moderate subdural hemorrhage and the brain showed severe contusions and diffuse hemorrhage throughout. The first four and the sixth ribs on the right side were fractured and both lungs showed severe general contusions, subpleural laceration and localized consolidation. The cause of death was given as pneumonia following laceration of the lungs and contusion of the brain from injury to the head.

Histologic Examination.—Choroid Plexus: Minor changes were present in the stroma of the plexus. In many localities the tufts retained their normal morphologic appearance. The blood vessels were small and empty. Only an occasional "fibrin thrombi" and no psammoma bodies were found. The epithelial margins were practically normal in outline. Only a few vacuoles were found in the epithelial cells and those were small. Thirty-three per cent of the cells were vacuolated. The average height of the choroidal epithelium was 11.78 microns. The only abnormality of the epithelial cells was the occasional occurrence of small vacuoles in the distal end of the cell. The basement membrane had been fairly well preserved.

Ependyma: Aside from a few scattered vacuoles the ependyma showed nothing abnormal.

Comment.—This patient died of a gas bacillus infection of the arm and pneumonia nine days after injury. The brain showed marked petechial hemorrhages but the choroid plexus presented only moderate changes. The ependyma likewise showed practically no change.

CASE 58.—*Basal fracture of the skull; death in twenty-seven hours.*

A man, aged 47, was injured at 2 p. m. on Dec. 10, 1927, in an automobile collision. He was taken to the Emergency Hospital where he died at 5:30 p. m. on December 11.

The coroner's examination revealed lacerations and contusions of the scalp, face and extremities. On opening the head a fracture was found running from the posterior right floor of the right middle fossa, and the roof of both orbits of the eyes was slightly fractured. On opening the body the lungs were found to be deeply congested and contused in several areas. The cause of death was given as fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: Extensive edema of the plexus stroma was present; it was diffuse in some places while in others the fluid seemed to have collected in large spaces. So-called "fibrin thrombi" were present but not numerous. The blood vessels were moderate in size and empty. The choroidal epithelium showed an increase in the number of vacuoles, but these were not large. Forty-four per cent of the cells were vacuolated, many of the vacuoles containing pigment. Some pigment in fine granules was also found in the stroma. The average height of the choroidal epithelium was 13.58 microns. The basement membrane was irregular and torn in most places.

Ependyma: The subependymal stroma was looser than usual and the ependymal epithelium was moderately vacuolated, especially adjacent to the area in which it became continuous with the choroid plexus.

Comment.—This case showed a rather extensive edema of the choroid plexus stroma, with a moderate increase in vacuolization (44 per cent). The choroidal epithelium cells were moderately heightened (13.58 microns). A moderate increase in the subependymal edema and increased vacuolization of the ependymal cells were also present.

CASE 59.—Basal fracture of the skull; concussion and contusion of the brain; death in three days.

A man, aged 61, was injured in an automobile accident at 8 a. m. on Dec. 10, 1927. He was rendered unconscious immediately and never regained consciousness. The bones of the left leg were fractured. On December 12, a right subtemporal decompression revealed a tight, dry brain. He died at 6:20 a. m. on December 13.

The coroner's examination showed extensive lacerations of the scalp. A fracture was found running from the occipital protuberance forward through the outer part of the left half of the occiput, across the left petrosal bone at its outer end and extending by two lines across the floor of the left middle fossa of the skull. The anterior portion of the right anterior lobe of the brain and the lateral surface of the left posterior lobe were contused and lacerated. A decompression operation had been performed on the right side. The left leg and the third to the sixth ribs on the left side were fractured. The cause of death was given as fracture of the base of the skull with other injuries.

Histologic Examination.—**Choroid Plexus:** Moderate edema of the stroma was present. The blood vessels were empty and not unusually distended. Throughout the field numerous "fibrin thrombi" were found. The free epithelial margin was not unduly irregular. A small amount of free blood was seen in the intervillous spaces. The epithelial cells contained various-sized vacuoles, some of which contained pigment. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 13.41 microns. The basement membrane was fairly well preserved in most places.

Ependyma: The ependyma showed no increase in vacuolization and appeared normal throughout its extent.

Comment.—In spite of death after three days, the choroid plexus and ependyma showed little change. From the clinical course one would look for much more marked changes at this time. The tight, dry brain at the time of operation gave evidence that an excess of cerebrospinal fluid was not present in the form of edema. It would seem that cerebral edema accompanies an increase in the activity of the choroid plexus.

CASE 60.—Basal fracture of the skull, with subdural hemorrhage and fractured pelvis; death within one hour.

A man, aged 40, was struck by an automobile at 1:55 p. m. on Dec. 12, 1927. He was picked up dead within a few minutes.

The coroner's examination revealed lacerations and abrasions of the scalp and face, associated with orbital hemorrhage. A fracture was found running along

the midline of the occiput into the foramen magnum, also a fracture of the roof of the right orbit. There was extensive subdural hemorrhage on the left side of the brain. On opening the body the left ramus of the pubic bone was found to be fractured, with laceration of the adjacent soft tissues. The cause of death was given as fracture of the base of the skull with fracture of the pelvis.

Histologic Examination.—Choroid Plexus: Moderate diffuse edema was found involving the stroma of the entire plexus. The blood vessels were open and empty. A few "fibrin thrombi" were found here and there in the section and a large number of psammoma bodies were found in the pedicle of the plexus. The free margin of the epithelium was irregular owing chiefly to enlargement of the individual cells. In some the distal portion of the cell assumed a lacelike appearance owing to the presence of numerous fine droplets. The vacuoles were fairly numerous and many of them contained a brownish, granular pigment. Forty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.05 microns. The basement membrane in many places could not be clearly made out because of the accumulation of fluid beneath the epithelium.

Ependyma: The ependyma showed no deviation from its normal morphologic appearance.

Comment.—This case showed moderate diffuse edema with increased vacuolization of the cells (44 per cent). The vacuoles in this instance were very small and numerous. Perhaps that is the way vacuoles form, i. e., by the coalescence of small droplets. The latter predominated in this case. It is also possible that when the activity is greatest the fluid passes through in the form of small droplets, a true cellular edema.

CASE 61.—*Basal fracture of the skull with subdural hemorrhage; death in twenty-two hours.*

A man, aged 47, was injured at 8:30 a. m. on Nov. 16, 1927, in an automobile collision. He was momentarily unconscious, but recovered consciousness later and was able to talk. After eight hours he became drowsy, the right pupil was dilated and Cheyne-Stokes respiration set in with deep coma. Roentgenograms showed a linear fracture on the right side. A right subtemporal decompression was performed and a subdural hemorrhage drained. He died at 6:25 a. m. on November 17.

The coroner's examination showed an extensive contusion of the scalp behind and above the right ear. A large subdural hemorrhage was found covering the surface of the right anterior hemisphere of the brain and an extradural clot in the right middle fossa of the skull. There was a comminuted fracture in the floor of the right middle fossa extending across the body of the sphenoid bone and also upward to the opening made by the decompression. The cause of death was given as comminuted fracture of the base of the skull.

Histologic Examination.—Choroid Plexus: A moderate generalized edema of the stroma was present. The blood vessels were open and empty. Coarse granular pigment was found throughout the section and was practically confined to the epithelium. The free margin of the epithelium almost everywhere presented a dentate appearance owing to a swelling of the distal portion of certain cells. The vacuoles were not abundant but were fairly large; most of them contained granular pigment. Thirty-four per cent of the cells were vacuolated. The average height of the choroidal epithelium was 15.60 microns. The detail of the basement membrane seemed to be lost in most places owing to the increase in fluid in the connective tissue stroma.

Ependyma: There was an accumulation of fluid in the subependymal tissue and for a short distance the ependyma was definitely vacuolated. A small amount of coarse granular pigment was found in the ependymal cells. There was some accumulated debris on the ependyma, apparently in the nature of degenerating red blood cells. This seemed to be emphasized by the fact that black pigment was present, some of which was contained within macrophages. Furthermore, the ependymal cells in these regions seemed to be distorted and the detail was obscured by the presence of this debris as well as subependymal fluid.

Comment.—In this case a large subdural hemorrhage was found at operation. The choroid plexus showed a moderate increase in edema and vacuolization. The ependyma showed marked blood pigment being taken up by macrophages, a picture suggestive of Essick's¹⁹ work.

NORMAL CHOROID PLEXUS

The normal choroid plexus (fig. 1), as studied in the ten patients who died of conditions that were remote and in no way influenced the central nervous system, was found to agree in practically all respects with the accepted descriptions of this structure. While the cells showed some variation in height (from 8 to 12 microns) in different portions of the plexus, such as the terminal tufts as compared with the pedicle, in similar areas they were uniform in size and showed only a slightly irregular free margin (fig. 2). It was generally observed that the cells were higher in children than in adults. The structure of each cell was typical, being columnar with a slightly rounded free distal end and a flattened proximal end lying on the basement membrane. The oval nucleus was found in the proximal portion of the cell with its long axis parallel to the long diameter of the cell. The nuclei were uniform in size and had a distinct nuclear membrane and an abundant, evenly distributed chromatin content. The cytoplasm of the cell was finely granular, the granules being evenly distributed in all portions of the cell. We found no evidence of a division into a basilar granular zone and a distal clear zone as described by Pettit and Girard.²⁰ Vacuoles were present in from 10 to 22 per cent of the cells; they were usually small and sharply outlined and lay in apposition to the nucleus. Occasionally, small, brownish-black pigment granules were found in the vacuoles. The basement membrane appeared as a well defined, even line which separated the cytoplasm of the cell from the subjacent stroma. It is not unlikely that this is formed of a heavy cell wall rather than being an additional structure. The stroma consisted of a few strands of connective tissue lying between the basement membrane and the blood

19. Essick, C. R.: Formation of Macrophages by the Cells Lining the Sub-arachnoid Cavity in Response to the Stimulus of Particulate Matter, *Contrib. Embryol.*, no. 42, Washington, Carnegie Institution, 1920.

20. Pettit and Girard (footnote 7, second reference).

vessel. Nuclei of connective tissue cells were found in small numbers in this stroma. The blood vessels in the terminal tufts were small and capillary in nature, being formed of endothelial cells. In most instances they were empty and round, evidently owing to the previous embalming.

We have noticed that in general the older the subject the more likely it is to find psammoma bodies or calcospheres, which usually occur in the pedicle of the plexus. They probably correspond to the so-called "fibrin thrombi," irregular masses of fibrinous material in the blood vessels of the tufts of the plexus. Such masses are shown to contain

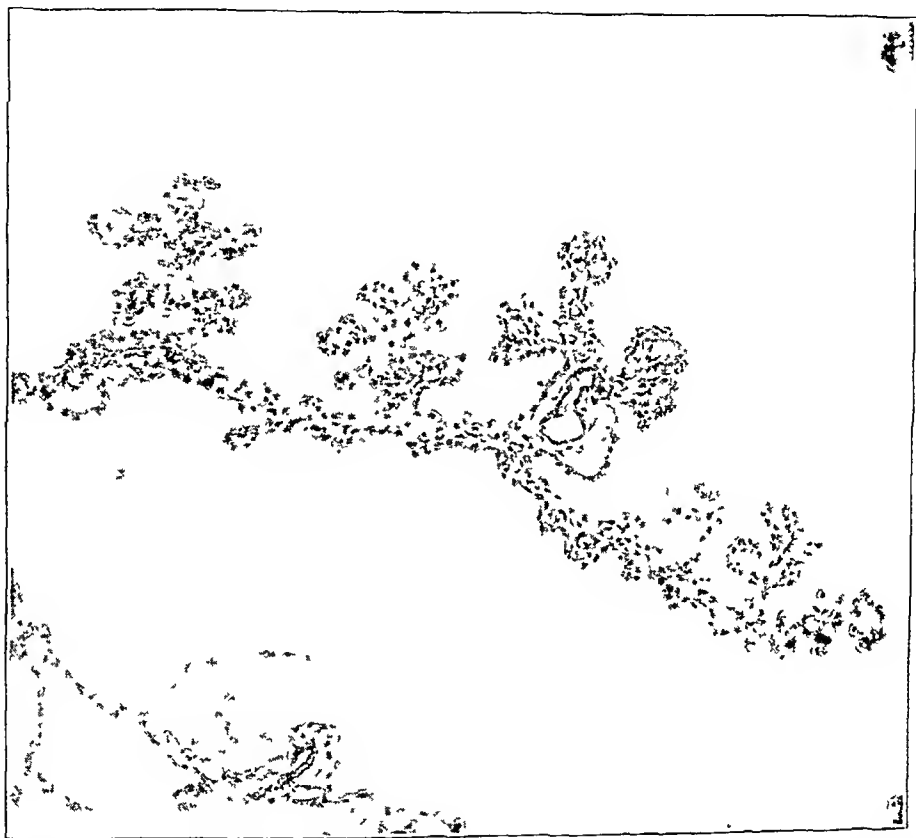


Fig. 1.—Normal choroid plexus. The connective tissue stroma forms an inconspicuous part of the structure. Consequently, the epithelial cells on either side of the villus are practically in apposition, except where separated by blood vessels. Hematoxylin and eosin; reduced from $\times 200$.

iron by the Prussian blue method. We believe that they have nothing to do with the injury to the head, but that they are evidence of a regressive change in the plexus, the causes of which are not clear.

HISTOPATHOLOGIC CHANGES

Definite changes have been found in practically all the constituents of the choroid plexus following trauma. In general the free epithelial

margin has shown greater irregularity in outline than is seen in that of a normal choroid plexus. In places the free border appears regularly serrated, owing perhaps to the increased height of the individual cells (fig. 3). This increase in height is thought to be due to an accumulation of fluid in the cell. It may represent edema of the cell, or may take the form of discrete vacuoles. Less commonly the free epithelial margin is actually ragged and torn. This is due to an actual destruction or tearing of the free margin, and not infrequently tags of cytoplasm may be seen swimming free in the ventricular space. These



Fig. 2.—Normal choroid plexus. The connective tissue is confined to a few small compact strands lying between the basement membrane and the wall of the blood vessel. A few vacuoles are seen in the epithelial cells. Hematoxylin and eosin; reduced from $\times 680$.

fragments may become detached and rounded, and may resemble the so-called "hyaline bodies" which some writers have described as occupying the space adjacent to the free margin. We have not observed any true hyaline bodies, but have seen these rounded structures which we could not distinguish morphologically from red blood cells. The free margin is more apt to be ragged, with numerous small vacuoles rupturing through it into the ventricle, than showing a single large vacuole. The latter, however, may give a torn appearance if it breaks

through the margin. In view of the work of Pettit and Girard,²¹ as well as that of Meek²² and others who described a marginal clear zone and a basal granular zone in what they considered to be actively secreting choroid epithelium, we have looked for similar observations in this series. However, we have rarely, if ever, observed this lack of granules in the apical part of the cells. In only one instance did it seem to be present, but in this case the edge, although lighter, was ragged as though it had been broken up with apparent loss of the smooth free margin of the cell.

Careful measurement of cells in certain areas was made in every case in this series. They differed greatly in height. In various cases

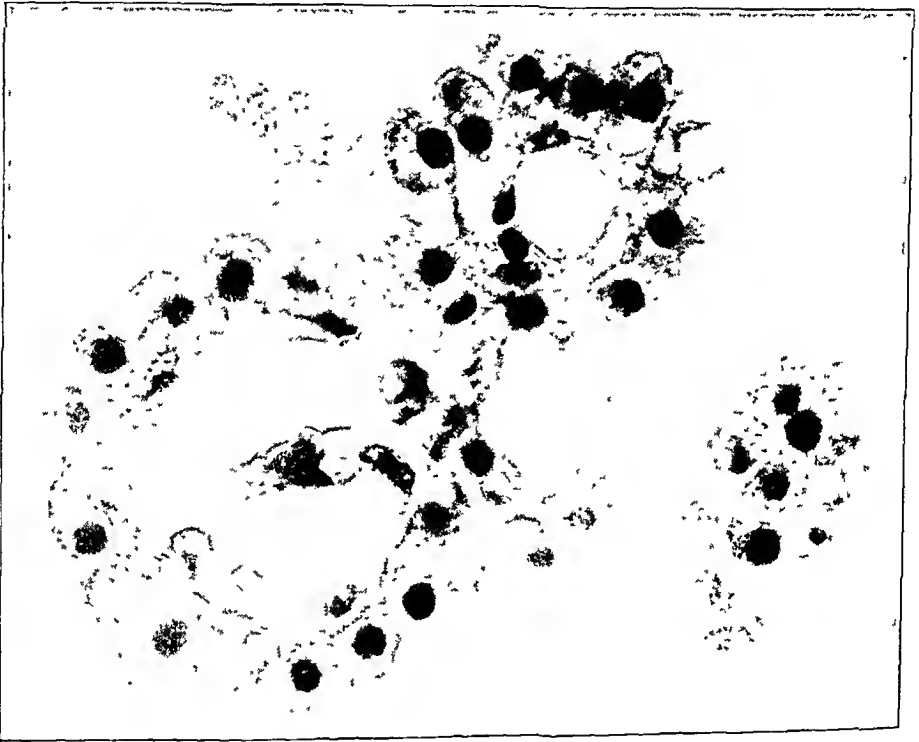


Fig. 3.—Vacuolization and serrated appearance of choroidal epithelium in case 3. There is an increase in the number of vacuoles in the epithelial cells. Some are also seen between the cells and along the basement membrane. At the upper right, one large cup-shaped vacuole is seen rupturing into the ventricular space. The free border is irregular or serrated, owing to uneven swelling of the individual cells. Death in ten hours. Hematoxylin and eosin; reduced from $\times 1,320$.

they averaged from 12 microns, which we considered a high normal measurement, to 20 microns in height in advanced edema. In a few instances epithelial cells of gigantic proportions were found. These

21. Pettit and Girard (footnote 7, first reference).

22. Meek, W. J.: A Study of the Choroid Plexus, *J. Comp. Neurol.* **17**:286, 1907.

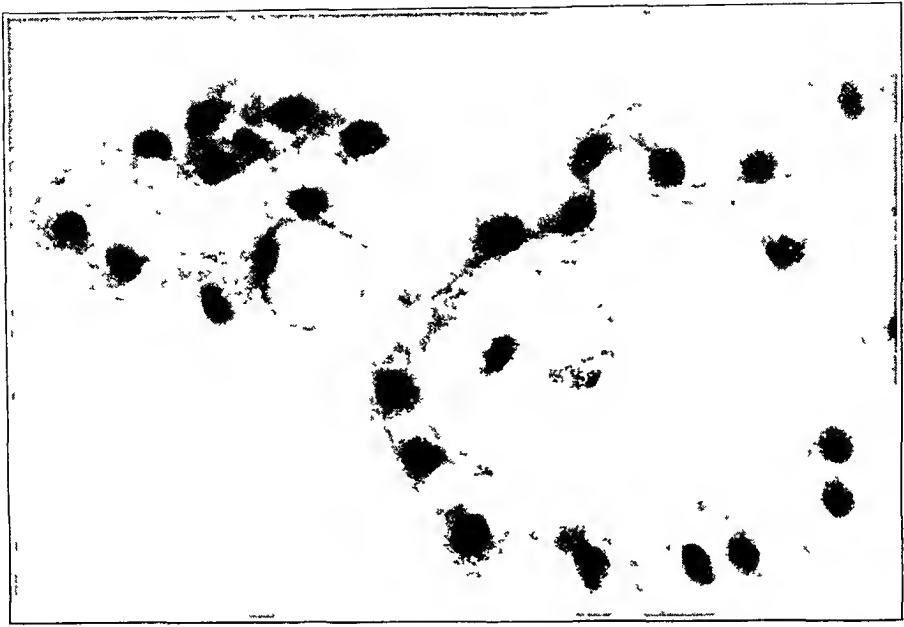


Fig. 4.—Vacuolization of choroidal epithelium in case 1. Unusually large vacuole about to rupture. A large vacuole adjacent to the basement membrane is also shown. Tremendous diffuse edema of the stroma is seen in the larger villus. Death in four hours. Hematoxlin and eosin; reduced from $\times 1,360$.

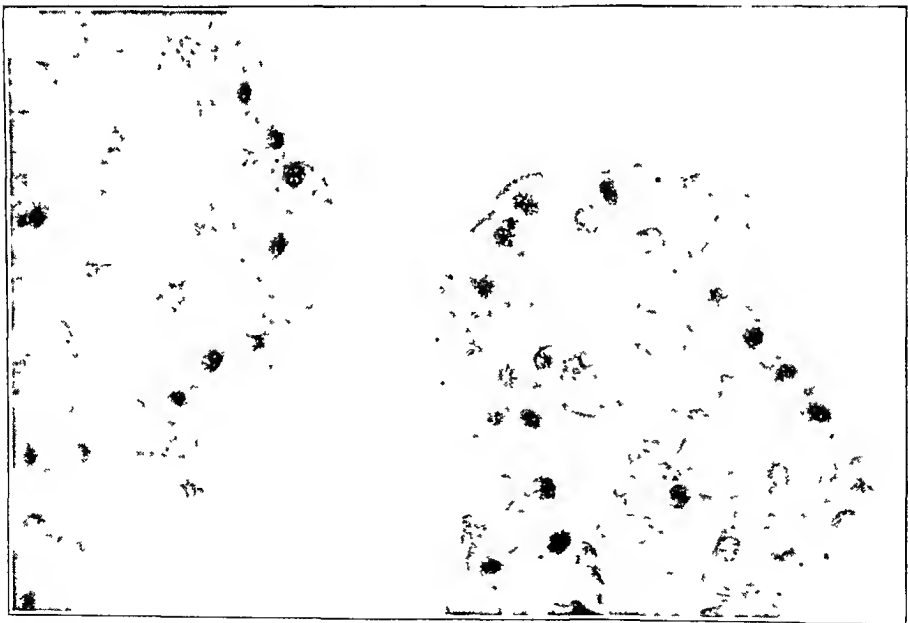


Fig. 5.—Vacuolization of choroidal epithelium in case 1. Very large vacuoles are found causing a disruption of the internal architecture of the cell. The irregularity of the basement membrane is evident. Marked generalized edema of the stroma in both villi is seen. Death in four hours. Hematoxylin and eosin; reduced from $\times 860$.

measured from 26 to 27 microns in height, being easily two or three times as large as an epithelial cell of a normal choroid plexus. In many instances the measurement did not represent the true height of the cell, because the free margin was ragged and had undergone rupture and loss of substance. This could be seen many times when the process of secretion was rapid. This was particularly true when the individual cell was filled with numerous small vacuoles which seemed to have torn through its free margin. Findlay⁶ has mentioned the presence of numerous small vacuoles which he believed on occasion coalesced to form larger ones.

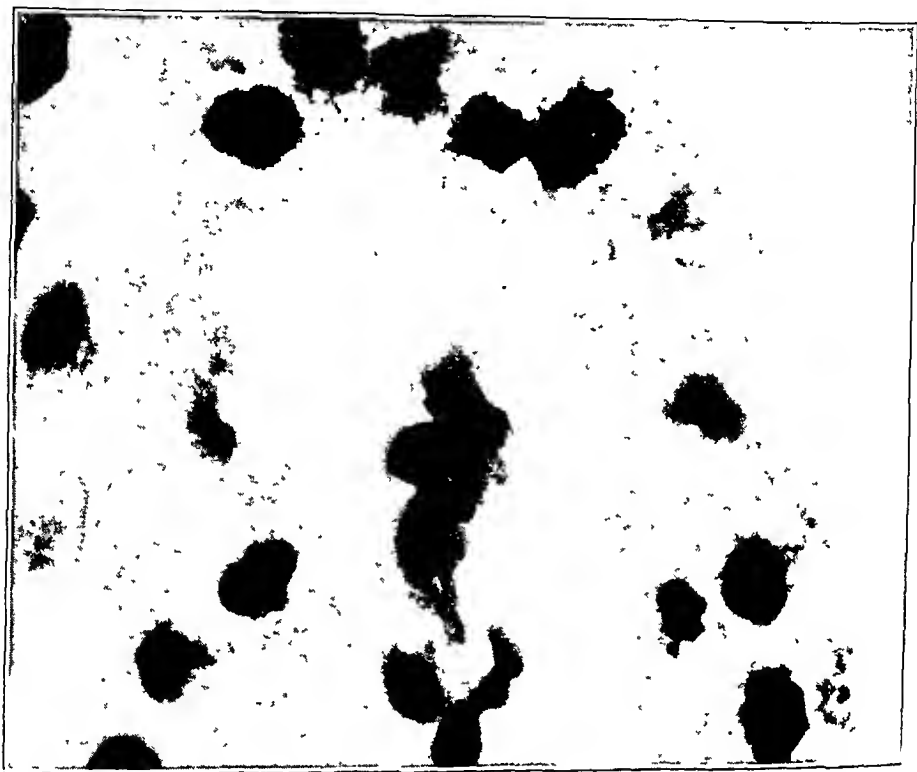


Fig. 6.—Vacuolization of choroidal epithelium in case 13. Epithelial cells loaded with minute vacuoles. A very narrow distal clear zone is seen. The connective tissue of the villus is compressed and the basement membrane is distorted by a collection of fluid. Death within three hours. Hematoxylin and eosin; reduced from $\times 2,960$.

Vacuoles of two varieties have been found, either a single large one or numerous small ones. We have thought that the presence of a single vacuole represented a relatively slow process in the activity of the cell (fig. 4). In such cases the morphologic appearance of the cell seems to be fairly well preserved and there is little evidence of destruction of the cytoplasm or alteration of the nucleus. In some cases more than one of these large vacuoles coalesced to form a large, smooth-walled.

irregular space. Again, the cell was sometimes tremendously distended with a large irregular space occupying its center and suggesting in miniature the ragged walls of a cyst (fig. 5). In the majority of cases there was a predominance of numerous small vacuoles which appeared as minute rounded clear spaces in the cytoplasm of the cells (fig. 6). These were either spread evenly throughout the cell or predominated at its free margin. We have considered this type of vacuolization as representing a more rapid metabolic process. In such instances the cytoplasm was more broken up and the free cell margin presented a

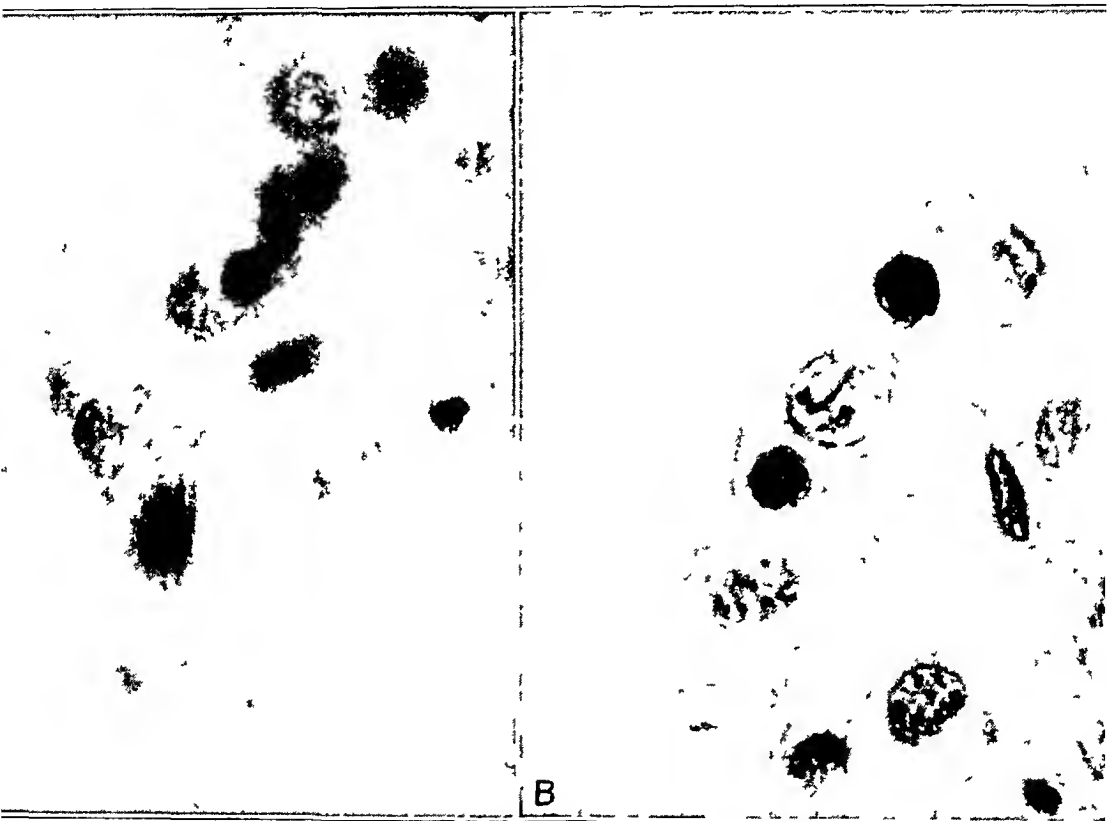


Fig. 7—*A*, rupture of nuclear membrane, and *B*, horseshoe-shaped nucleus in case 24. Death two days after injury. Hematoxylin and eosin, reduced from $\times 1,800$.

ragged appearance with bits of cytoplasm hanging in tatters in the ventricular space.

The nature of these vacuoles has given rise to much discussion. Do they represent active secretion of the cell? Most observers believe that they do. On the other hand, Becht¹⁶ pointed out that they may represent absorption of fluid from the ventricle into the choroid plexus. He noted that actively secreting cells in certain other glands, such as the parotid, are smaller than quiescent ones, and consequently he did not

believe that an increase in the vacuolization and the size of the choroid epithelium necessarily indicates increased secretion. By analogy, he held that the cells should actually be smaller than normal during activity.

It has seemed to us that these vacuoles must be fluid containing both in the normal choroid and in the choroid following trauma. We do not believe that they are hyaline bodies or fat globules. When hyaline stains, such as van Gieson's stain, are used they still appear as clear spaces in the cell. Likewise we were unable to demonstrate the presence of fat in the vacuoles. With fat stains, such as Nile blue or



Fig. 8—*A*, vacuolization of nuclei of epithelial cells in case 15. Death within three hours. *B*, nucleus enclosed in large vacuole in case 3. Death after ten hours. Hematoxylin and eosin; reduced from $\times 1,800$.

scarlet red, Sundwall²³ also was unable to demonstrate fat in the choroid plexus of the ox.

Granulation of the cell cytoplasm was variable in amount, depending on the nature of the metabolic process. If this was slow the normal granular appearance of the cells was preserved. If there were a large number of minute vacuoles they gave an appearance of increased granu-

23. Sundwall, J.: The Choroid Plexus with Special Reference to Interstitial Granular Cells, *Anat. Rec.* **12**:221, 1917.

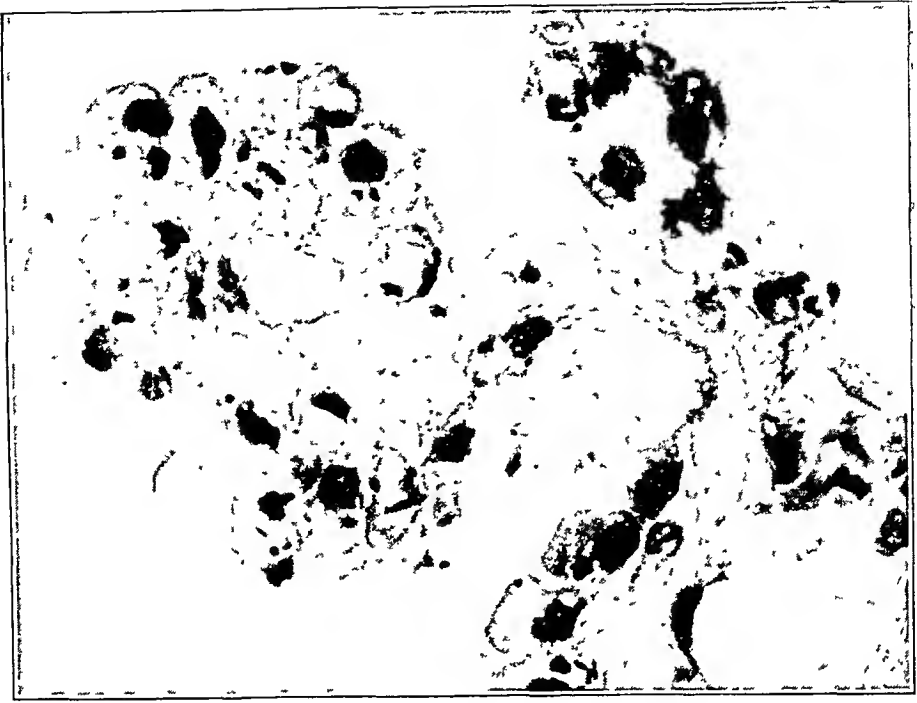


Fig. 9.—Pigmentation of choroidal epithelium in case 13. Practically all of the cells are vacuolated in this villus and most of them contain granular pigment. In one instance it is projecting into the ventricle. Death within three hours. Hematoxylin and eosin; reduced from $\times 1,400$

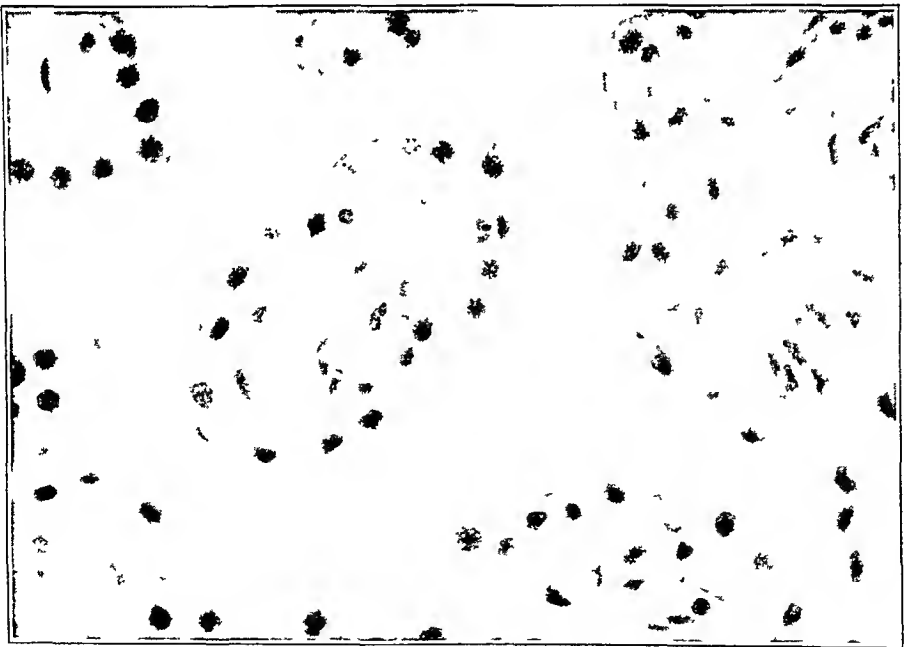


Fig. 10.—Collections of fluid in stroma in case 35. Local collections of fluid in the stroma which have distorted and compressed the basement membrane of the epithelial cells. Death within one hour. Hematoxylin and eosin; reduced from $\times 340$

lation of the cell. In reality, we believe, they represented increased vacuolization. When a group of cells was cut in cross-section they often seemed to be separated by irregular fluid spaces, the nature of which was not entirely clear.

Changes in the morphologic appearance of the nuclei of the choroid epithelium were often seen.* Usually the nucleus was swollen moderately and at times markedly. Again vesiculation was present. When the nucleus was greatly swollen actual rupture of the membrane with scattering of the chromatin content into the adjacent cytoplasm was occasionally observed (fig. 7A). In other instances there was a shrinkage and distortion of the nucleus with the chromatin material



Fig. 11.—Moderate edema of stroma in case 3. Death ten hours after injury. This degree of edema is fairly characteristic of most of our cases. Hematoxylin and eosin; reduced from $\times 200$.

condensed into an irregular shape, the particles being large and closely packed together. In other cases nuclear distortion took place without appreciable swelling or shrinkage of the structure. This characteristically took the form of a pseudopod suggesting the outline of a gourd. In some cases the handle was bent around so that the whole nucleus was horseshoe-shaped (fig. 7B). In some instances, especially where the process was rapid and associated with numerous small vacuoles in the cytoplasm of the cell, the nuclei also became vacuolated (fig. 8A). The vacuoles either were in the form of a single round or oval body, or were dumb-bell shaped. In some instances it was possible to see

invaginations into the nuclear membrane from an adjacent vacuole in the cytoplasm. This would suggest that it may be the method of vacuole formation as well as of nuclear distortion, although it does not explain all the pictures observed in the latter instance. Findlay⁶ likewise described vacuolization of the nuclei of the choroid epithelium. At times we have seen the nucleus lying entirely external to the cell in the free ventricular space. A nucleus has also been observed lying entirely within a large vacuole (fig. 8B).

Pigmentation is present in a minor degree in the normal choroid plexus of man. In this series the pigment was often found to be increased, usually being present in vacuoles (fig. 9). It occurred in the shape of irregular stars or crystals with bizarre shapes and sharp or

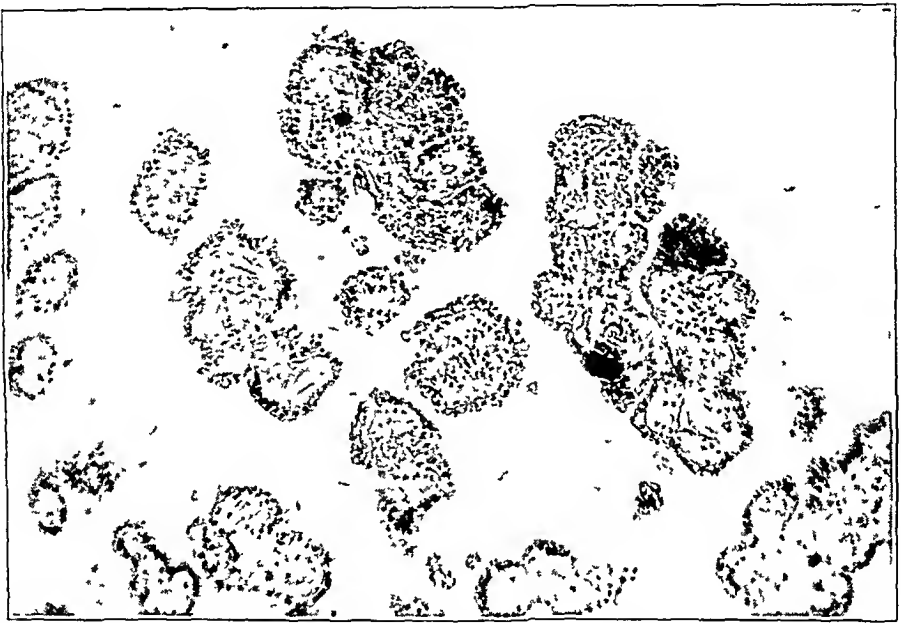


Fig. 12.—Extensive edema of stroma in case 1. This degree of edema was present in only four cases. It usually occurs from two to four hours after injury. Death within four hours. Hematoxylin and eosin; reduced from $\times 200$.

irregular points. It was usually located in the periphery rather than the center of a vacuole. This might suggest that it did not float in the fluid, but sank to the most dependent portion. Flather,²⁴ in writing of the pigmentation found in animals, called it hemosiderin. In our cases iron was not shown by the potassium ferrocyanide test, although it was present in the fibrin masses both within and without the blood vessels. We have felt that the pigment was iron-free, possibly hematoidin. In

24. Flather, M. D.: A Study of the Hemosiderin Content of the Choroid Plexus, *Am. J. Anat.* **32**:125 (Sept.) 1923.

some instances the choroid epithelium was found to be broken up, and bits of pigment were seen in its margin or lying free in the ventricular cavity. Pigmentation was not confined to the choroid epithelium, but was also present in lesser amounts in the stroma of the plexus.

Normally the basement membrane is preserved intact. This was true in our series when the accumulation of fluid was moderate in degree and in the form of small globules. In such cases fluid spaces were usually present between the basement membrane and the wall of a blood vessel. When the process was more extensive and probably more rapid, the free fluid was found in large spaces in the stroma and the basement membrane was often torn. In certain instances it was greatly



Fig. 13.—Hemorrhage into stroma in case 19. Extensive hemorrhage into edematous stroma. The red blood cells are well preserved. Diffuse pigmentation of the stroma and the choroidal epithelium. Death after ten hours. Hematoxylin and eosin; reduced from $\times 860$.

distorted or even destroyed, so that the inferior aspects of the cells were extremely irregular and appeared as though fluid were pushing into or between them (fig. 10). In slower processes vacuoles were found which indented the basement membrane and pressed into the base of the cell. More characteristically the first indication of the passage of fluid through the cell was a flattened vacuole lying along the basement membrane or less commonly along the lateral cell wall. As the vacuole increased in size, it became more rounded and came in contact with the inferior aspect of the nucleus. The nucleus at times was indented by

the vacuole, much like the basement membrane described. These basilarly situated vacuoles suggest the canaliculi which Sundwall²³ found in the choroid plexus of the ox.²⁵

The connective tissue of the stroma is inconspicuous in the normal choroid plexus. After injury various degrees of edema were observed. These were most striking under lower magnification. In some instances there was but minor separation of the fibrous constituents and only small collections of fluid were found in the stroma (fig. 11). In others the swelling was more diffuse and distention reached tremendous

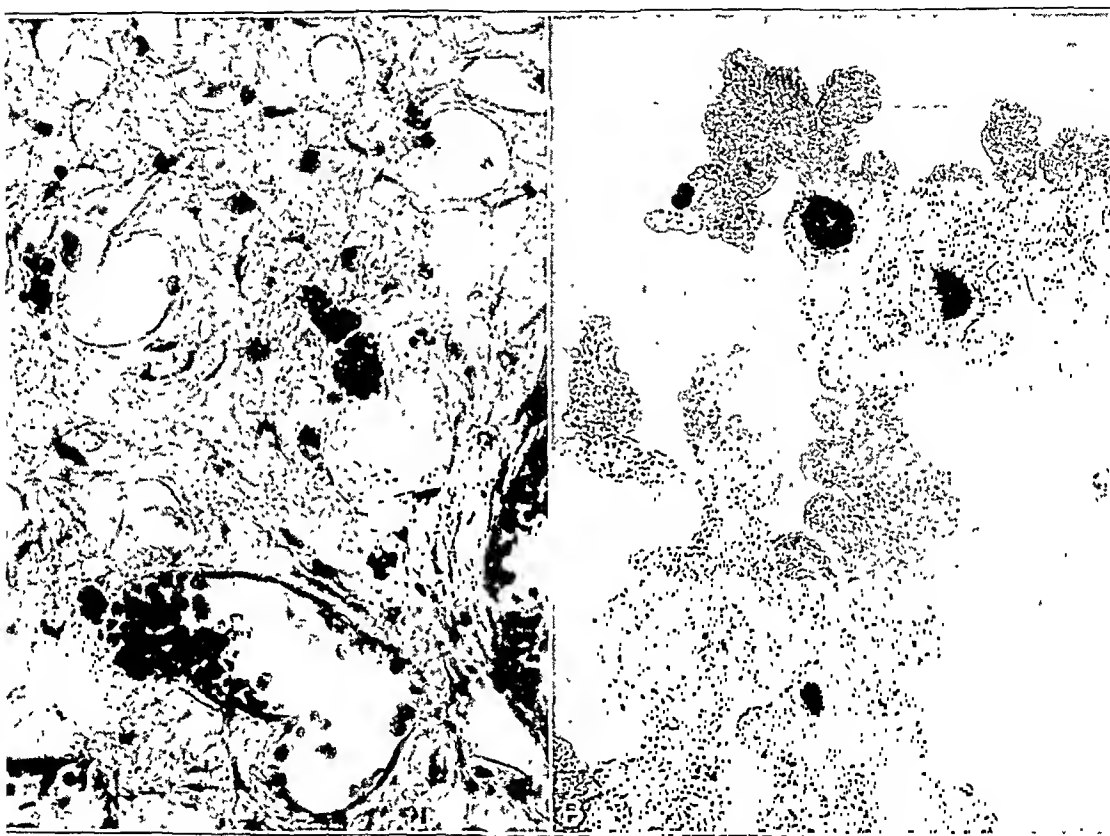


Fig. 14.—*A*, phagocytosis of pigment in stroma in case 22. Death in five days. Hematoxylin and eosin; reduced from $\times 560$. *B*, pigment in choroid plexus in case 19. Death in ten hours. With the Prussian blue method, calcospheres stained deep blue and small pigment granules brown; reduced from $\times 95$.

proportions (fig. 12). The fluid at times accumulated in large spaces in various portions in the stroma, but characteristically between the

25. The question arises whether Sundwall was describing normal or traumatic choroid plexuses, as the method of slaughtering oxen is usually by striking on the head with a sledge hammer. If this was the method of killing employed, the animal would certainly suffer a concussion and contusion of the brain and present pathologic changes in the choroid.

blood vessels and basement membrane. These collections of fluid at times took the form of numerous small droplets. When they became enlarged the smaller individual septums were broken down so that extensive spaces were found. From our observation in several cases showing early changes it would seem as though fluid may collect in the loose connective tissue of the stroma before it appears as vacuoles in the choroidal epithelium. Hemorrhage at times occurred in the stroma, often with the red blood cells well preserved (fig. 13).

Certain changes were found in the connective tissue cells. If the edema of the stroma was moderate the nucleus might be swollen so that



Fig 15—Wandering cells in stroma in case 41. The edematous stroma contains many leukocytes. There was no gross evidence of meningitis in this case. Death in three and a half days. Hematoxylin and eosin, reduced from $\times 450$.

it appeared vesicular or more rounded than normal. It was normally oval and much elongated. In other cases the nuclei took peculiar shapes with indentations and projecting pseudopodia. The cells and nuclei were occasionally vacuolated. If the nuclei became vesicular the chromatin assumed a circular arrangement as in plasma cells. Pigmentation was often present in the stroma, in which case the pigment granules were contained in phagocytic cells or sometimes appeared even in the leukocytes (fig. 14*A*). Noniron-containing pigment was demonstrated by the specific potassium ferrocyanide test (fig. 14*B*). Findlay⁶ likewise described pigment as being present in phagocytic

cells of the stroma, as well as within vacuoles of the choroid epithelium. Masses of "fibrin," referred to by us as "fibrin thrombi," were sometimes found outside as well as inside the lumen of the vessels.²⁶ These took a deep bluish purple with the routine stains. With the iron stains, i. e., potassium ferrocyanide, they were found to contain much iron in their meshes. In some cases these "fibrin thrombi" were numerous and formed a conspicuous feature in the low power magnifications. They were usually found to be more numerous in older persons. Osnato and Giliberti²⁷ mentioned the occurrence of these "fibrin thrombi" and concluded that their presence is due to a disturbance of the colloidal equilibrium of blood calcium, favoring its precipitation. Psammoma bodies



Fig. 16.—Wandering cells in stroma and ventricles in case 40. Extensive infiltration of leukocytes in choroid plexus in a clinical case of meningitis following injury. Death in nineteen days. Hematoxylin and eosin; reduced from $\times 200$.

were also frequent in the pedicle of the choroid plexus and likewise increased in number as age advanced. The blood vessels were usually distended, owing largely to preliminary embalming. This also explained

26. Because these structures are found in normal as well as in abnormal choroid plexuses, their presence is not indicative of previous trauma. It is evident from their situation and incidence, as well as from their staining reaction, that they are closely related to the psammoma bodies that occur in the pedicle of the plexus.

27. Osnato, M., and Giliberti, V.: Postconcussion Neuroses; Traumatic Encephalitis: A Conception of Postconcussion Phenomena, *Arch. Neurol. & Psychiat.* 18:181 (Aug.) 1927.

the fact that most of them were empty, as the blood had been washed out by this process. At times the nuclei of the endothelial cells of the vessels were swollen and vesicular. This was considered as secondary to edematous and hyperemic changes in the choroid plexus.

In many cases round or polymorphonuclear leukocytes were seen in the stroma of the choroid plexus (fig. 15). They were often present microscopically, even when meningitis was not observed grossly or present clinically. They were, of course, always found in greater numbers when meningitis was present clinically (fig. 16).

The normal ependyma (fig. 17) consists of a single layer of epithelial cells of the squamous or cuboidal type, attached to the underlying substance of the brain by a delicate basement membrane. However, as the choroid plexus is approached these cells become more columnar.



Fig. 17.—Normal ependyma. Cells are cuboidal, having an indistinct basement membrane. A few small vacuoles can be seen between the nuclei in several cells. They are normally present in small numbers in the ependyma. Hematoxylin and eosin; reduced from $\times 1,400$.

The low normal or squamous type has been found to measure approximately 5 microns in height. The cuboidal type varies from 6 to 9 microns in height, and the columnar type averages from 11 to 13 microns. Normally they may contain a few vacuoles. Their nuclei are oval and occupy a position near the base of the cell with the long diameter corresponding to that of the cell. A thin indefinite basement membrane can be made out in places. This in part may be composed of the basal lining of the cells themselves. The subependymal tissue usually shows little edema and does not tend to distort the alignment of the basement membrane.

Following injury we found changes in the ependyma in many respects closely resembling those seen in the choroid plexus. The

epithelial cells were swollen in proportion to the edema present. Often they were from two to three times as high as a normal cell, some individual cells measuring as much as from 30.1 to 30.25 microns. The nuclei were often pushed to a distal position in the cells by the underlying wall of advancing fluid, so that they gave a palisaded appearance (fig. 18). The fluid often formed a line of vacuoles behind them. Again they were pushed about in an eccentric manner by the vacuoles in the ependymal cells. These vacuoles at times literally tore the cells to pieces and little was left except the tattered margin and the displaced nucleus. It is possible that the whole cell, including the basement membrane, was pushed far forward in some instances. The basement mem-

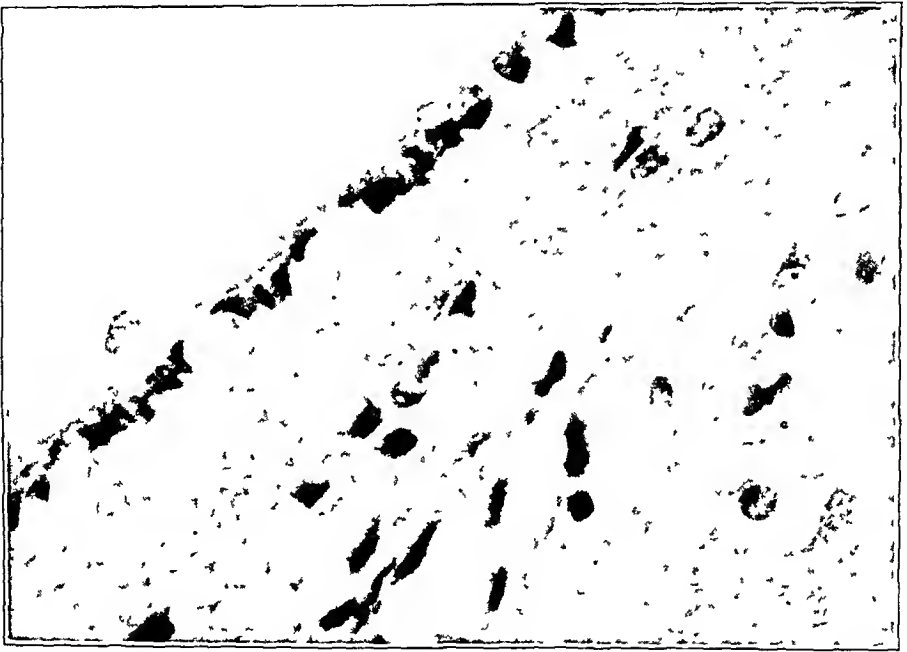


Fig. 18.—Moderate vacuolization of ependymal epithelium in case 11. Most of the fluid is in the base of the cells, apparently pushing the nuclei forward and giving a palisaded appearance. Death in twenty hours. Hematoxylin and eosin; reduced from $\times 1,400$

brane was usually distorted and was often broken or entirely destroyed by the fluid pressure from below. The subependymal tissue likewise showed varying degrees of fluid distention. In minor or moderate cases it was but little changed, with perhaps some increase in the size of the interstitial spaces. In "full blown" edema, however, the intercommunicating septums were entirely torn apart so that great lakes of fluid often could be seen piling up behind the ependymal lining (fig. 19). On occasion the ependymal cells were separated so that fluid could be seen passing between them. In cases of bleeding into the ventricle, a layer of

broken-down red blood cells in various degrees of degeneration could be seen clinging to the free margin of the ependymal lining (fig. 20).

INTERPRETATION OF OBSERVATIONS

In reviewing this series of cases, it seems to us that the increased vacuolization, both of the epithelium of the choroid plexuses and of the ependyma, suggests that these structures are capable of secretion of fluid. If this is true it is further evidence that the choroid plexuses in particular are the chief sources of cerebrospinal fluid. It seems logical to conclude that following severe injuries to the head, the activity of the choroid plexuses as well as of the ependyma is stimulated. This



Fig. 19.—Marked vacuolization of the “full blown” ependyma in case 24. The cells are markedly distorted by the large vacuoles. One of them appears to have broken through into the ventricles. The subependymal tissue appears to be definitely edematous. Death two days after injury. Hematoxylin and eosin; reduced from $\times 1,400$.

probably accounts for the excess of cerebrospinal fluid found clinically in such cases. This process apparently starts immediately following an injury and proceeds with varying intensity until the death of the patient or until his recovery begins. On occasion it is undoubtedly influenced by other concomitant factors, such as alcoholism, meningitis, ventricular hemorrhage, decompressive operations or the employment of hypertonic solutions in treatment. From an experimental standpoint the intravenous use of hypertonic solutions apparently retards the activity of the gland while the administration of hypotonic solutions, as shown by

Weed²⁸ and Ferraro,²⁹ stimulates it. In Ferraro's series of rabbits, in which hypotonic solutions were introduced intravenously, the vacuolization of the choroid plexus was greatly increased. Edema of the stroma was also present. In his animals there were large collections of fluid in the ependymal cells as well as an increase in the vacuolization of the subependymal tissues. His observations were practically identical with, although more extensive than, those made in this series. This is to be expected, as it is possible to produce more marked edematous changes in the "water brain" of the rabbit than would reasonably follow trauma in man. In our series of cases in which intravenous injections of hypertonic dextrose solution were given, the changes in the choroid plexus

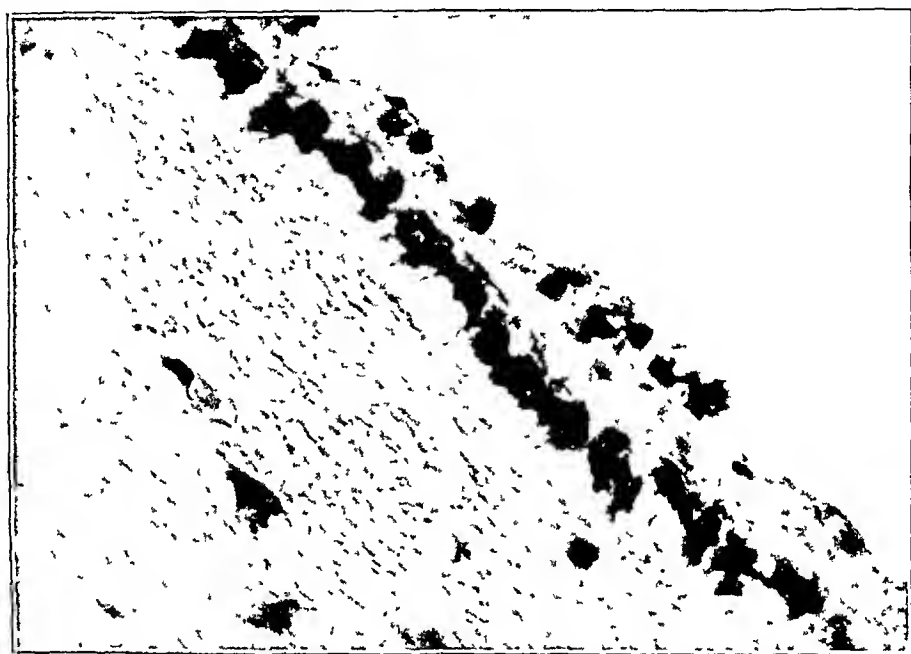


Fig. 20.—Vacuolization of ependymal cells and ventricular hemorrhage in case 10. Vacuolization of ependyma is moderately increased, the fluid vesicles displacing and distorting the nuclei. Red blood cells in various stages of degeneration are found along its free margin. Grossly the ventricles were filled with blood. Death within twenty minutes. Hematoxylin and eosin; reduced from $\times 1,400$.

and the ependyma were less marked than otherwise. The greatest degree of change was found in the patients who died from two to four hours after injury to the head. Practically none of these patients received hypertonic dextrose solution. It would be interesting to

28. Weed, L. H.: The Effects of Hypotonic Solutions upon the Cell-Morphology of the Chorioid Plexuses and Central Nervous System, *Am. J. Anat.* **32**:253 (Sept.) 1923.

29. Ferraro, A.: The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, *J. Nerv. & Ment. Dis* **71**:129 (Feb) 1930

speculate as to what extent changes may occur in the choroid plexuses and ependyma in nonfatal cases.

In attempting to interpret our observations, the normal physiologic process of the choroid plexus is a constantly recurring question. Whether the cerebrospinal fluid is formed by a process of secretion, excretion or dialyzation has not been answered. If it is a secretion, as we have come to believe, two mechanisms for the formation of this fluid may be considered. Is it a result of selective activity of the choroidal epithelium or is it a vasomotor phenomenon? Findlay⁶ and Mott³⁰ both described nerve fibers in the choroid plexuses of the calf, sheep and man. These are in the neighborhood of the blood vessels of the stroma and take a plexiform arrangement. They were not able to demonstrate terminal fibrils to the epithelial cells themselves. From a histologic standpoint it seems that the blood vessels of the choroid are equipped with a vasomotor control. Whether the secretion of cerebrospinal fluid depends wholly or in part on vasomotor activity is an unsettled question. However, the presence of such nervous elements suggests a function of some sort, although as yet this function is unknown. It may be that increased production of fluid by the administration of vasodilators, such as pilocarpine and ether, may result from an increase in blood flow to the plexuses. It is further possible that the increase in fluid production following injury to the head may be due to a paralytic action on the vasoconstrictors either directly or perhaps indirectly through a secondary substance, as has been suggested in the production of local edema of peripheral soft tissues after injury.

CONCLUSIONS

1. Increased vacuolization of the choroidal epithelium together with heightening of the individual cells is usually found following fatal injury to the head. This may occur in the form of single large circumscribed vacuoles or as numerous small droplets giving the impression of cellular edema. These changes vary within wide limits, and, beginning immediately, apparently reach their maximum in from two to four hours following injury. Other factors, such as shock, the time interval between injury and death and the use of hypertonic dextrose solution, undoubtedly influence the ultimate picture. By analogy, it may be assumed that similar changes occur in nonfatal cases.

2. A variable degree of edema of the stroma takes place under these circumstances. It is felt that this edema probably precedes the changes in the epithelial cells. On occasion, hemorrhagic extravasations are

30. Mott, F. W.: The Pathology of the Cerebro-Spinal Fluid, *Lancet* 2:1 and 79, 1910.

observed, but more frequently one sees pigment in the stroma and epithelial vacuoles, which may indicate disintegration of red blood cells. We believe that this pigment is hematoidin.

3. Subependymal edema, as well as an increase in the vacuolization and the height of the ependymal cells, often occurs. These changes are variable in degree and are not as constant as those found in the choroid plexus.

4. The changes are similar to those found in the "water brain" of animals produced experimentally by the intravenous injection of hypotonic solutions.

5. Whether the changes observed are due to selective activity of the epithelial cells or are secondary to vasomotor phenomena is as yet undetermined.

THE SIGNIFICANCE OF FAT EMBOLISM *

B. M. VANCE, M.D.

NEW YORK

INTRODUCTION

Fat embolism is that condition which occurs when a liquid oil enters the circulating blood and is transported in globules large enough to obstruct the lumen of blood vessels in different parts of the body. It has been described frequently as an important complication of trauma in human beings, and occasionally may be severe enough to be a definite cause of death. Two well defined clinical and pathologic varieties of fat embolism are now recognized: (1) the pulmonary form, in which the emboli obstruct the smaller blood vessels of the lungs and produce symptoms of asphyxia, and (2) the cerebral form, in which the emboli gain entrance to the arterial circulation, block the arterioles in the different organs, especially the brain, and produce symptoms referable to the central nervous system.

Fat embolism of a less serious nature has been found at necropsy not only in persons who have suffered from trauma, but in others who do not give a traumatic history. At the present time, while it is recognized that the condition is a definite result of injury, many believe that it can occur from other causes.

I have made an attempt to discover how far this belief is correct. The literature on fat embolism is reviewed briefly, and a number of routine necropsies of the Office of the Chief Medical Examiner of New York are studied for the purpose of ascertaining the incidence and importance of this condition.

The subject has been subdivided for convenience into the following parts:

Fat Embolism in Human Pathology: Etiology.

Fat Embolism in Human Pathology: Clinical Signs and Pathologic Lesions:

(a) Pulmonary Fat Embolism.

(b) Systemic or Cerebral Fat Embolism

(c) Diagnosis and Treatment of Fat Embolism.

Fat Embolism in Animal Experiments.

Comment and Summary.

FAT EMBOLISM IN HUMAN PATHOLOGY; ETIOLOGY

In the literature, two main classes of conditions are associated with fat embolism. The first category includes true etiologic factors, such

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* From the office of the Chief Medical Examiner of New York.

as traumas to the adipose tissues of the body and the intravenous injection of oily substances. The second category comprises a variety of processes which have been mentioned as causative agents but which have a doubtful significance in this respect.

The true etiologic factors are classified as follows:

Traumas to the adipose tissue:

1. Trauma to the osseous system
 - (a) Fractures of the bones
 - (b) Jarring of the skeleton
 - (c) Orthopedic operations
2. Trauma to subcutaneous and intermuscular fat
3. Trauma to fatty viscera

Intravenous injection of various oils

The dubious etiologic factors are:

1. Burns
2. Postmortem processes
3. Poisons
4. Natural causes of death

TRAUMAS TO ADIPOSE TISSUE

Fat embolism is produced by physical injury to fatty tissue only when the three conditions enumerated by Gauss¹ are present: 1. The force must so injure the envelop of the fat cell that liquid fat is set free. 2. The force must tear small veins in the vicinity of the liquid fat. 3. Some mechanism must be present which will drive the liquid fat into the open ends of the torn veins and so introduce it into the general venous circulation. These factors operate in all cases of fat embolism due to trauma, but are especially applicable when the skeletal bone marrow is involved.

1. *Trauma to the Osseous System*.—A consideration of the structure of the long bones and the fatty bone marrow is necessary for a proper understanding of the close connection of skeletal injuries and fat embolism.

In normal infancy and childhood the long bones are easily bent and contain a red cellular marrow throughout. According to Landois² the fat present is composed of the less fluid oils, such as palmitin and stearin, with a smaller proportion of the more fluid olein. The architecture of the bone is more homogeneous, and the transition from the

1. Gauss, Harry: The Pathology of Fat Embolism, Arch. Surg. 9:592 (Nov.) 1924.

2. Landois: Deutsche med. Wchnschr. 52:283 (Feb. 12) 1926.

dense bone of the shaft to the cancellous bone of the extremities is more gradual than in adult skeletons.

By the usual process of growth, the cellular bone marrow becomes more and more fatty and the proportion of olein increases so that the oil is quite fluid at body temperature. The shaft and epiphyses are more clearly separated in structure, as the latter are composed of spongy cancellous bone filled with fatty marrow, while the shaft is a hard tube of dense bone, surrounding a friable vascular fatty marrow. All these anatomic peculiarities are important factors in the causation of fat embolism.

(a) *Fractures of the Shafts of the Long Bones:* The most frequent cause of fat embolism is fracture of the shaft of a long bone, especially in the lower extremity. Numerous reports have testified abundantly to this lesion as an important etiologic factor from the time of Busch,³ in 1865, to the present day.

There are good reasons why fat embolism should accompany this type of injury. In the first place, many fat cells are ruptured and an appreciable amount of liquid oil is set free around the ends of the broken bones. As Gauss¹ pointed out, many veins are torn across, especially those in the haversian canals which are enclosed in a rigid tube of bone and cannot readily collapse. According to Bergemann,⁴ the natural aspirating force of the veins will remove such liquid fat as may be set free and transport it to the main venous circulation and hence to the lungs. Any increase of internal tension in the area of injury, such as might occur from a marked hemorrhage or reflex spasm of the muscles of the extremity, will only increase the absorption of fat and, as a result, the severity of the embolism. The experiences of Siegmund,⁵ Sutton⁶ and others have established these facts beyond dispute.

According to Landois,² most of the serious cases of fat embolism after fracture occur in men between the ages of 20 and 50. Not only are these the years during which trauma is most likely to occur, but they are also the period when the bone marrow is especially fatty and contains the highest percentage of olein. As this oil is quite fluid at body temperature, it is more easily absorbed than the more viscous fats, palmitin and stearin, which are present in the fat in normal children. It is probably for this reason that a serious grade of fat embolism does not complicate fractures in children to the same degree as in adults.

3. Busch, F.: *Virchows Arch. f. path. Anat.* **35**:321, 1866.

4. Bergemann, E.: *Berl. klin. Wchnschr.* **47**:1112 (June 13) 1910.

5. Siegmund, H.: *München. med. Wchnschr.* **65**:1076 (Sept. 24) 1918.

6. Sutton, George E.: *Brit. M. J.* **2**:368 (Oct. 15) 1918.

(b) Concussion or Jarring of the Skeleton: A few instances of severe fat embolism have been described in which the skeleton was subjected to a severe jarring without, however, fracture of the bones. In the case of Ziemke,⁷ the casualty suffered was a fall from a height; a fall on an amputation stump was described by Beitzke;⁸ a heavy blow on the right knee occurred in the case of Busse;⁹ the patient of Ribbert¹⁰ suffered an unknown injury of which the only trace was a small bruise on the right hip; and in the case of Frauendorfer¹¹ the patient fell into a pool at the moment an underwater bomb was exploded.

Except in the case of Frauendorfer, lesions of the bones and bone marrow were not described. This investigator noted a large number of lentil and pea-sized hemorrhages scattered through the fatty bone marrow, which he regarded as the result of the violence inflicted on the skeleton by the explosion. He also believed them to be the source of the fat emboli.

Schultze¹² offered a plausible explanation of the mechanism by which such hemorrhages are produced. The sudden jarring separates small portions of the flaccid fatty marrow from the firm bony cortex, ruptures a few fat cells and tears a few arteries and veins in the affected area. Numerous small hemorrhages then occur and raise the pressure inside the bony cavity, thus forcing liquid fat into the torn veins and so into the circulation.

(c) Orthopedic Operations: Various operations on bones and joints for the correction of deformities and other morbid conditions have frequently caused a fat embolism with fatal results. In a few instances the condition was due to open operations, as in Lucke's¹³ case of resection of the hip joint, Vogt's¹⁴ case of resection of the knee joint and Kirschner's¹⁵ case of osteotomy. The bloodless correction of old joint contractures, especially about the knee, was made responsible for the same complication in the reports of Colley,¹⁶ Lymphius,¹⁷ Eberth,¹⁸ Payr,¹⁹ Clarke²⁰ and others.

7. Ziemke: *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **1**:193, 1922.

8. Beitzke: *Centralbl. f. allg. Path. u. path. Anat.* **24**:824 (Sept. 30) 1913.

9. Busse: *Cor.-Bl. f. schweiz. Aerzte* **43**:154 (Feb. 1) 1913.

10. Ribbert, Hugo: *Cor.-Bl. f. schweiz. Aerzte* **24**:457 (Aug. 1) 1894; *Deutsche med. Wchnschr.* **26**:419 (June 28) 1900.

11. Frauendorfer, Otto: *Beitr. z. gerichtl. Med.* **6**:1, 1924.

12. Schultze, Ernst O. P.: *Arch. f. klin. Chir.* **111**:573, 1918-1919.

13. Lucke: *Centralbl. f. Chir.* **6**:719 (Nov. 1) 1879.

14. Vogt, P.: *Centralbl. f. Chir.* **10**:377 (June 16) 1883.

15. Kirschner, M.: *Centralbl. f. Chir.* **51**:465 (March 15) 1924.

16. Colley, Fritz: *Deutsche Ztschr. f. Chir.* **36**:322, 1893.

17. Lymphius, M.: *Centralbl. f. Chir.* **23**:800 (Aug. 15) 1896.

18. Eberth, J. C.: *Fortschr. d. Med.* **16**:251 (April 1) 1898.

19. Payr, E.: *München. med. Wchnschr.* **45**:885 (July 12) 1898.

20. Clarke, B. Earl: *Fat Embolism, J. A. M. A.* **88**:919 (March 19) 1927.

In short, fat embolism is accepted as a possible serious complication of orthopedic operations and is considered by many as referable, not only to the necessary trauma of the operation, but also to the abnormal conditions of the bones and bone marrow of the patients. Generally the skeletal deformities lead to prolonged rest in bed and disuse of the extremities, with the result that the marrow soon becomes fatty and the bone soft and osteoporotic. The manipulations during the operation cause considerable distortion of the bone, a general rise of intra-osseous pressure and rupture of fat cells and veins. Conditions are thus favorable for the introduction of fat into the circulation. In a few instances injuries of the soft parts, muscular tears, epiphyseal separations and actual fractures serve to increase the intensity of the embolism.

2. Trauma to the Adipose Tissue of the Skin and Intermuscular Areas.—Injuries that rupture the subcutaneous and intermuscular fat cells not infrequently cause a fat embolism of a severe grade, as the same mechanisms operate just as they do in the case of skeletal injuries. Cases of this sort were described by Flournoy,²¹ Pinner²² and Buerger.²³

The case of Buerger²³ was a good example of injury to the subcutaneous fat, in which a fat embolism is especially likely to develop. A woman, aged 72, was beaten with a club, and suffered extensive separation of the dermis from the muscular fascia. The subcutaneous fat was torn, forming large pockets full of blood and oil. No fractures were noted. At necropsy, the lungs contained a large number of fat emboli.

Injuries to the pelvic fatty tissue by the passage of the fetal head through the birth canal are said to cause fat embolism. Cases of this sort were reported by Warthin²⁴ and Virchow.²⁵

Operative incisions in the subcutaneous fat of obese persons were mentioned as a cause of fat embolism by Ferguson²⁶ and by Bissel.²⁷

3. Trauma to the Fatty Viscera.—In rare instances a fatty internal organ, such as the liver, may be ruptured and death may result not from shock or hemorrhage but from an extensive fat embolism. Cases of this kind were described by Hamilton²⁸ and Engel.²⁹ The latter

21. Flournoy: *Centralbl. f. Chir.* **5**:703 (Oct. 19) 1878.

22. Pinner, O.: *Berl. klin. Wchnschr.* **20**:185 (March 26) 1883.

23. Buerger: *Vrtljschr. f. gerichtl. Med.* **39**:159, 1910.

24. Warthin, Aldred Scott: *Internat. Clin.* **4**:171, 1913.

25. Virchow, R.: *Berl. klin. Wchnschr.* **23**:489 (July 26) 1886.

26. Ferguson, H. F.: *Brit. M. J.* **1**:584 (March 16) 1895.

27. Bissel, Wayne W.: *Surg. Gynec. Obst.* **25**:8 (July) 1917.

28. Hamilton, D. J.: *Brit. M. J.* **2**:474 (Oct. 6) 1877.

29. Engel, H.: *München. med. Wchnschr.* **48**:1046 (June 25) 1901.

suggested that the embolism was caused by compression which forced fat from the liver cells into the torn ends of the small venules of the liver.

Siegmund⁵ noted that fat embolism is occasionally associated with bullet wounds of the head which tear the brain tissue extensively. In these cases, however, the grade of the embolic process is usually slight.

INTRAVENOUS INJECTION OF VARIOUS OILS

The injection of oil intravenously will produce fat embolism, a fact that has been demonstrated repeatedly by experiments on animals. It is only rarely, however, that this is duplicated in human beings. According to Weingarten,³⁰ the hypodermic injection of oily substances therapeutically can produce a slight grade of fat embolism. Koch³¹ injected liquid human fat into a scar of the neck and elicited symptoms that suggested that a nonfatal grade of fat embolism had been produced. Fibiger³² described a case in a man who received 50 cc. of olive oil intravenously and who died as a result of the injection. Such examples of the condition, however, are exceptional as far as human pathology is concerned.

MORBID PROCESSES ASSOCIATED WITH FAT EMBOLISM:

DUBIOUS ETIOLOGIC FACTORS

Fat embolism has been described in connection with a variety of conditions with which, however, the etiologic relationship is not altogether obvious.

Burns.—Several investigators have found fat emboli in the pulmonary vessels of bodies that have been burned, and much controversy exists regarding the significance of this association. Olbrycht³³ claimed that fat embolism is caused solely by antemortem burns and only when the burning is more severe than the first degree. According to him, the heat renders the fat fluid and opens the smaller vessels so that it can gain entrance to the circulation. Others, including Groendahl,³⁴ Weimann³⁵ and Harbitz,³⁶ are inclined to question this interpretation, and to attribute the fat emboli to associated injuries. Groendahl pointed out that the degree of fat embolism described in cases of burn is usually slight and of minor importance.

30. Weingarten, R.: *Schweiz. med. Wchnschr.* 7:248 (March 20) 1926.

31. Koch, Herman: *Deutsche Ztschr. f. Chir.* 186:273, 1924.

32. Fibiger, quoted by Groendahl: *Deutsche Ztschr. f. Chir.* 111:56, 1911; and by Wegelin: *Schweiz. med. Wchnschr.* 4:133 (Feb. 8) 1923.

33. Olbrycht, J.: *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 1:642, 1922.

34. Groendahl, Nils Backer: *Deutsche Ztschr. f. Chir.* 111:56, 1911.

35. Weimann, W.: *Virchows Arch. f. path. Anat.* 264:1, 1927.

36. Harbitz, Francis: *Vrtljschr. f. gerichtl. Med.* 45:34, 1913.

Harbitz, however, mentioned that masses of liquid fat were found in the larger systemic veins of the trunk but not in the lungs in bodies that had been thoroughly cooked by flame. He expressed the belief that the process was caused entirely by the postmortem action of the heat which contracts the skin surface, liquefies the fat and forces it onward into the vessels.

Postmortem Processes.—According to Westenhoeffer,³⁷ a condition simulating fat embolism has been produced by the action of a post-mortem gas bacillus decomposition in the marrow cavity of the shaft of the long bones. In a woman who died as the result of a septic abortion, necropsy showed numerous fat globules in the pulmonary vessels. The long bones showed marked invasion by gas bacilli, which Westenhoeffer attributed to the fact that the marrow in this case was rich in cells and so was a good nutrient medium for the organism. The formation of gas increased the intra-osseous pressure, freed the fat from the cell envelop and forced it through the veins into the pulmonary vessels.

Neureiter and Strassman³⁸ pointed out that the fat emboli in Westenhoeffer's case could have been due to some antemortem process, but they believed that postmortem transportation of fat by gaseous decomposition is possible. Buerger,³⁹ on the other hand, regarded fat embolism as an intravital phenomenon in every case and declared a postmortem etiology unthinkable.

In any event, the degree of postmortem embolism is comparatively slight, and the validity of Westenhoeffer's theory has not been fully proved.

Poisons.—Fat embolism has been cited in connection with death from various poisons. Groendahl³⁴ mentioned poisoning by phosphorus, potassium chlorate, potassium bichromate, potassium cyanide, corrosive mercuric chloride, U. S. P., phenol and alcohol as the alleged causative factor, but he questioned any etiologic relationship between the poisoning and the embolism.

Puppe³⁹ described fat globules in the vessels of a person who died of subacute phosphorus poisoning. He believed that they were caused by fatty degeneration of normal white blood cells which coalesced inside the vessel and formed fat emboli.

MacMahon and Weiss⁴⁰ reported a fatal case of poisoning by carbon tetrachloride associated with a marked fatty degeneration of

37. Westenhoeffer, M.: Virchows Arch. f. path. Anat. **170**:517 and 528, 1902; Vrtljschr. f. gerichtl. Med., 1904, supp., p. 184.

38. Neureiter, F., and Strassman, G.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **1**:204, 1922.

39. Puppe: Vrtljschr. f. gerichtl. Med., 1896, supp., p. 94.

40. MacMahon, H. E., and Weiss, S.: Am. J. Path. **5**:623 (Nov.) 1929.

the liver and with a macroscopic demonstration of fat in the blood of the pulmonary artery. On microscopic examination, however, fat emboli were not found in the finer blood vessels of the lung, and a diagnosis of fat embolism was not made.

Winogradow⁴¹ discovered fat emboli in a case of poisoning by potassium chlorate and believed them to be due to multiple hemorrhages in the fatty bone marrow caused by the toxic action of the chemical.

Burns and Bromberg⁴² described a case of fat embolism in an obese colored woman who had received an injection of arsphenamine four days prior to death. No explanation was given for the fat emboli, but it is not at all probable that they were due to the toxic action of the drug.

From these cases it is obvious that intravascular fat has been demonstrated in deaths due to chemical poisons, but it is not as evident that the action of the chemical was the causative factor in the production of the embolism.

Natural Causes of Death.—Fat embolism has also been associated with many deaths from natural and nontraumatic causes. In the older literature, as cited by Scriba,⁴³ necrotic purulent foci and septic processes in general were supposed to produce severe grades of this condition. This was especially true when an osteomyelitis of the shaft of a long bone was the lesion in question, as it was usually accompanied by a rise of intra-osseous pressure which was supposed to force fat into the circulation. Others believed that the intravascular fat took its origin from fatty degeneration of thrombi or ulcerated areas on the vessel wall. At present, these theories are not taken seriously.

Jurgens⁴⁴ and Virchow,⁴⁵ considered that eclampsia caused fat embolism through multiple venous ruptures in the liver combined with fatty degeneration of the parenchyma cells which allowed liquid fat easily to enter the venous blood. Virchow, however, did not exclude injuries to the pelvic fat from childbirth as a cause of the emboli. It is possible that the fat emboli noted in connection with eclampsia may be due to some traumatic factor apart from the toxemia.

Diabetes mellitus, with lipemia, is supposed to produce intravascular fat similar to fat embolism, owing to the coalescence of the fine lipemic emulsion into larger droplets. Fischer,⁴⁵ Ebstein,⁴⁶ Saundby and Barling⁴⁷ described cases of this kind. Graham,⁴⁸ however, claimed

41. Winogradow, B.: Virchows Arch. f. path. Anat. **190**:92, 1907.

42. Burns, E. L., and Bromberg, L.: Am. J. Syph. **14**:43 (Jan.) 1930.

43. Scriba, J.: Deutsche Ztschr. f. Chir. **12**:118, 1880.

44. Jurgens: Berl. klin. Wchnschr. **23**:519 (Aug. 2) 1886.

45. Fischer, Bernhard: München. med. Wchnschr. **69**:814 (June 2) 1922.

46. Ebstein, W.: Virchows Arch. f. path. Anat. **155**:571, 1899.

47. Saundby and Barling: Brit. M. J. **1**:781, 1882.

48. Graham, G. S.: J. M. Research **11**:459, 1907.

that there is no similarity between the microscopic picture of the intravascular fat in diabetic lipemia and true fat embolism. It is not at all evident that the fat droplets in cases of fat embolism are derived from a lipemic condition of the blood.

Several investigators, including Katasa,⁴⁹ Olbrycht,³³ Weingarten,³⁰ Lehman and McNattin,⁵⁰ examined the lungs for fat embolism during a large number of routine necropsies in cases not associated with severe trauma. A definite proportion of positive observations were recorded, the highest of which was 50 per cent (Lehman and McNattin) and the lowest 7 per cent (Katasa).

Many of Katasa's series showed definite disease of the kidneys, and he was inclined to see a connection between the renal lesion and fat embolism. As Weingarten noted, however, care was not taken to exclude definitely slight traumas of different sorts, hypodermic injections of therapeutic oils and the like, which would be sufficient to account for the slight degree of fat embolism that was found.

Freak cases, interesting pathologically but of slight clinical importance, have been reported. Heitzmann⁵¹ mentioned the instance of a man who died of gangrene of the lung following pneumonia; at necropsy fat emboli were found in the capillaries and the arterioles of the spleen and kidney, but not in the lung. This was explained by the fact that fatty debris had been aspirated from the gangrenous area through the pulmonary vein and transported to the left side of the heart and the arterial system. Groendahl³⁴ described fat emboli confined to the radicles of the portal vein in the liver, which he believed originated in one instance from a fat necrosis of the pancreas, and in another from trauma to the mesenteric fat involved in intussusception of the intestines.

A perusal of the literature suggests that while fat embolism is most often the result of injury to adipose tissue, examples of this condition have been recorded in which the history of trauma was not clear. The question then arises concerning the origin of the intravascular fatty globules; are they or are they not always the result of trauma?

An attempt was made to answer this question by studying a series of 246 necropsies, which occurred among the routine examinations of the Office of the Chief Medical Examiner of New York City. Sections of the lungs and kidneys from each necropsy were preserved in a solution of formaldehyde, sectioned on the freezing microtome and stained with sudan III. The sections were examined under the microscope for

49. Katasa, A.: *Cor.-Bl. f. schweiz. Aerzte* 47:545 (May 5) 1917.

50. Lehman, E. P., and McNattin, R. F.: *Fat Embolism*, *Arch. Surg.* 17:179 (Aug.) 1928.

51. Heitzmann: *Centralbl. f. allg. Path. u. path. Anat.* 28:405 (Aug. 31) 1917.

fat emboli, and the diagnosis was made only when it could be definitely determined that the globule of intravascular fat was blocking the lumen of the arteriole or capillary.

The lungs and kidneys were chosen for this purpose because the presence of emboli in the lungs showed definitely that the liquid fat had entered the pulmonary circulation, while their presence in the kidney served as a convenient indication that the systemic circulation had been invaded.

The interpretation of results was necessarily qualitative. In the sections from the lung five degrees of fat embolism were recorded: (1) very slight, (2) slight, (3) moderate, (4) severe and (5) fatal. The degree was designated as very slight and slight when fat emboli

TABLE 1.—*Degree of Pulmonary Fat Embolism in Various Types of Injury*

Injuries	Negative Results	Very Slight	Slight	Moderate	Severe	Fatal	Total
Fractures of skull.....	8	5	8	3	0	0	24
Fractures of skull and ribs.....	2	3	1	0	0	0	6
Fractures of skull, ribs and clavicle.....	0	0	5	0	0	0	5
Fractures of skull and lower extremity.....	1	1	4	0	0	1	7
Fractures of femur.....	5	0	1	2	1	1	10
Fractures of pelvis.....	3	2	1	10	3	0	19
Fractures of tibia and fibula.....	5	2	2	0	2	1	12
Multiple fractures of lower extremity.....	1	0	0	3	1	0	5
Fractures of ribs and lower extremity.....	0	1	0	3	2	0	6
Fractures of ribs.....	0	0	4	2	0	0	6
Fractures of upper extremity.....	0	1	3	2	1	0	7
Injuries to soft parts of leg.....	2	1	0	1	0	0	4
Fractures of spine.....	1	0	2	4	0	0	7
Fractures of lower jaw.....	1	0	0	0	0	0	1
Bullet wounds.....	6	2	0	1	0	0	9
Stab wounds.....	6	0	0	0	0	0	6
Internal injuries.....	2	2	3	1	0	0	8
Scalp laceration.....	1	0	0	0	0	0	1
General lacerations.....	2	0	0	0	0	0	2
Manual strangulation.....	3	0	0	0	0	0	3
Head injury with subdural hemorrhage.....	3	0	0	0	0	0	3
Contusion of anterior abdominal wall.....	0	0	0	1	0	0	1
Operations.....	10	0	0	0	0	0	10
Orthopedic operations.....	6	0	0	1	1	0	8
Total.....	62	20	34	34	11	3	164

were found only occasionally in the section: as moderate when the emboli were numerous but did not occur in alarming numbers, and as severe and fatal when the embolism was excessive and dangerous to life.

Fat emboli were found in the kidneys only in a few cases of the severe and fatal types. They were never present when the lungs showed only a mild grade of embolism. They are not listed in the tabulations.

No attempt was made to demonstrate fat in the blood of the pulmonary artery macroscopically by the method described by Bacon and LeCount.⁵² The conditions under which the necropsies were performed rendered the production of artefacts only too likely and would have given too many erroneous results.

52. Bacon, L. H., and LeCount, E. R : Automobile Injuries, Arch. Surg. **18**: 769 (March) 1929.

The 246 necropsies are separated into those associated with physical trauma, which numbered 164 cases, and those not associated with physical trauma, which numbered 82 cases. The first category is represented in table 1. The age and sex are not shown on the chart as the figures had little bearing on the results, and it is sufficient to mention that the male sex predominated and that the age at which the injuries were most prevalent was from 20 to 60 years.

According to table 1, the type of injury had a great deal of influence on the production of the emboli. Fractures of the skeleton, especially of the bones of the lower extremity, were marked by a greater incidence and a more severe grade of fat embolism than were other forms of trauma. As a general rule, the more severe the violence that produced the fracture the more consistent was the appearance of the emboli in the lungs.

TABLE 2.—*Degree of Fat Embolism in Fractures of the Lower Extremity*

	Nega- tive	Very Slight	Slight	Moder- ate	Severe	Fatal	Total
Patients dying at scene of accident.....	1	2	0	3	0	0	6
Patients dying in 1 to 24 hours.....	1	2	4	11	5	0	23
Patients dying in 1 to 7 days.....	3	1	4	4	4	3	19
Patients dying in 7 to 14 days.....	3	0	0	0	0	0	3
Patients dying in 14 to 21 days.....	1	1	0	0	0	0	2
Patients dying after 21 days.....	6	0	0	0	0	0	6
	15	6	8	18	9	3	59

In the cases of fracture of the lower extremity, there were indications that most of the fat embolism was caused by aspiration of liquid fat into the circulation at the site of injury through the torn ends of the small veins. Investigation of the region of the fracture, especially in persons who had survived the violence only a few minutes, disclosed from 40 to 60 cc. of liquid fat mixed with blood around the ends of the broken bones. When the patient had lived longer the quantity of the extravasation was sometimes the same, but was usually much less. Apparently the amount taken into the circulation varied with the individual case, because fractures similar in other respects showed widely different degrees of fat embolism. The protective mechanisms of the organism against the aspiration of fat into the circulation, such as collapse of the veins or closure of the veins by the processes of repair, were more efficient in some instances than in others.

A measure of the efficiency of these mechanisms can be noted in table 2, in which fifty-nine cases of fracture of the lower extremity are listed. About 80 per cent of these were negative for fat emboli, or showed only a moderate number, while only 20 per cent displayed a serious degree of embolism.

The relationship between the degree of fat embolism and the length of time the patient lived after the injury is shown in table 2. Of forty-eight patients who died during the first week after the trauma occurred, forty-three had fat emboli and five did not. The more severe grades of the condition were found in those who lived from one to seven days. After the first week only one case of slight degree was noted. These facts suggest that the greatest amount of fat enters the circulation in the first seven days after the fracture, but that after this interval it is removed from the vessels in some manner.

In injury other than fracture, only six cases showed fat embolism of moderate grade or over. Of these one was the result of an injury to the soft parts of the leg, one was due to a ruptured liver, two were the result of orthopedic manipulations, and one was associated with a contusion of the anterior abdominal wall followed by a laparotomy. In

TABLE 3.—*Results of Examination for Fat Emboli in Absence of Physical Trauma*

	Negative	Positive	Total
Electrocution.....	1	0	1
Burns.....	3	0	3
Chemical poisons.....	16	1	17
Cases showing gas decomposition.....	2	0	2
Natural causes of death.....	33	6	39
			<hr/> 82

the sixth case a bullet wound of the retroperitoneal tissues and the inferior vena cava macerated the fat cells and allowed the liquid fat to gain entrance to the circulation through the hole in the vein. In spite of the fact that the patient died in a few minutes from hemorrhage, a moderate grade of pulmonary fat embolism was found.

In this series there was no instance of fat embolism that could be attributed to jarring of the skeleton. There was one case, however, in which lesions similar to those described by Frauenthorfer¹¹ were noted in the bone marrow. A man, aged 45, fell from a height, fractured his left thigh bone and died in a few minutes of shock. The right femur was not broken, but section through the shaft disclosed hemorrhagic areas, from 1 to 2 mm. in size, distributed through the fatty marrow. On microscopic examination, the fatty tissue was found to be torn from the bony trabeculae in these areas, with consequent extravasation of red blood cells.

The eighty-two cases that were not associated with physical trauma are listed in table 3.

The seven positive results were examples of a very slight fat embolism in the lungs. The kidneys were normal in every case.

The large number of negative results coupled with the few positive observations suggests that when death is not connected with physical trauma a fat embolism of a serious grade is not likely to develop.

The cases of burns were caused by flame in two instances and were of the third degree. The other burn was due to scalding water.

The cases of poisoning included eight of acute alcoholism, three of chronic alcoholism, one of alkaline corrosion of the stomach, one of arsphenamine poisoning, and one of illuminating gas poisoning, all of which were negative for fat emboli. The only positive result consisted of a very slight degree of fat embolism in a case of methyl alcohol poisoning, and the connection between the two conditions was dubious.

Of the fifty-nine cases in which death was due to natural causes, fifty-three were negative, and six positive, for fat emboli.

The cases giving negative results included ten of heart disease, four of chronic nephritis, three of advanced liver disease, twelve of pulmonary disease, six of cerebral conditions, six of sepsis following abortion, one of eclampsia, one of diabetes mellitus, two of pernicious anemia, one of pyelonephritis, one of mesenteric thrombosis, three of general carcinomatosis, one of intestinal obstruction and one case each of malnutrition and encephalitis, respectively, in children.

The cases giving positive results comprised two of chronic nephritis, one of pachymeningitis interna hemorrhagica, one of abscess of the brain, one of chronic duodenal ulcer and one of sepsis due to abortion.

The reason for the pulmonary fat emboli in these cases must be a matter of speculation, as a complete history could not be obtained. It is conceivable, however, that a slight injury of adipose tissue somewhere in the body during convulsions or therapeutic injections of oily liquids into a small vein by accident can produce this condition on occasion. In any event, the degree of the embolism in these cases was so slight as to be of little clinical importance.

The only conclusions to draw from these facts are that from 12 to 14 per cent of cases of nontraumatic death may show a slight grade of fat embolism. As a result, a slight grade of fat embolism cannot be considered a reliable indication of trauma. On the other hand, a severe or moderate grade of fat embolism is the result of an intravital injury and when demonstrated post mortem is sufficient proof that the trauma occurred prior to death.

FAT EMBOLISM IN HUMAN PATHOLOGY: CLINICAL SIGNS AND PATHOLOGIC LESIONS

After an injury when fat is absorbed into the blood the first stopping place is the lungs. These organs, as Fischer⁵³ pointed out, are capable of accommodating large numbers of fat emboli. Their reserve capacity is so great that it is only in severe cases that the embolism obstructs the pulmonary circulation. When this occurs, two eventualities present

53. Fischer, Bernhard: *Verhandl. d. deutsch. path. Gesellsch.* 17:279, 1914.

themselves, as Payr⁵⁴ first noted: 1. The patient will die as the result of asphyxia from the emboli in the lungs. 2. The emboli will be driven through the pulmonary vessels into the arterial side of the circulation where they will cause death by involving such important organs as the brain, heart and kidneys. Payr⁵⁴ termed the first outcome pulmonary fat embolism and the second, cerebral fat embolism.

PULMONARY FAT EMBOLISM

The symptoms of pulmonary fat embolism are referable to the obstruction in the pulmonary circulation which causes a marked decrease in the respiratory interchange in the alveoli. As a result the oxyhemoglobin content of the red blood cells is lessened and the carbon dioxide content of the plasma is increased. At the same time, the right side of the heart becomes engorged and is unable to force the blood onward. The supply of blood to the left side of the heart is curtailed, and the arterial blood pressure falls. The whole organism tends to suffer from the deficient oxygenation of the red blood cells and the disability of the circulation. In the end the interchange of oxygen in the tissues is damaged.

Groendahl⁵⁴ recognized two clinical varieties of pulmonary fat embolism: 1. The first type is marked by a violent onset of dyspnea attended by marked cyanosis and edema of the lungs which comes on suddenly a few hours after the injury. Death in these cases is rapid and is attributed to the fact that after the trauma large amounts of fat are absorbed rapidly. 2. The second type is slower in its development. An appreciable interval of from several hours to several days intervenes between the injury and the onset of the symptoms. After the trauma the patient may be quiescent or at the most show a few signs of restlessness and anxiety. A persistent cough then appears, accompanied by blood-tinged sputum, dyspnea, cyanosis and signs of edema. Toward the end the respiration becomes stertorous and passes gradually into the Cheyne-Stokes type. In this final stage coma develops which is referable in part to the asphyxia and in part to a disturbance of the cerebral circulation.

According to Groendahl,⁵⁴ the pulmonary type of fat embolism is likely to develop in patients whose myocardium is weak, especially on the right side of the heart. Many of these cases are found in elderly persons possessing, in addition to the cardiac disability, emphysematous lungs the capillaries of which are smaller than normal and so are more easily blockaded by the embolic fat. Groendahl claimed that dilatation of the right ventricle is found at necropsy in such cases. He contended that younger and stronger persons with an efficient heart muscle are

54. Payr, E.: *Ztschr. f. orthop. Chir.* 7:338, 1900.

more apt to force the fat onward into the general circulation, and are less likely to succumb to asphyxia.

The principal lesions in pulmonary fat embolism are in the lungs. On macroscopic examination these organs appear voluminous and cyanotic and show areas of aeration mingled with darker areas of congestion and edema, which are characteristic of asphyxial conditions in general. Small hemorrhages may occur in the pleura or in the septums of the lung; groups of alveoli may be filled with blood and appear under the pleura as small hemorrhagic foci. These lesions are supposed to be caused by the back pressure in the pulmonary circulation which ruptures small pulmonary vessels.

On microscopic examination fat emboli can be demonstrated in the arterioles and capillaries of the lungs in large numbers. In the arterioles they appear as spherical or ovoid globules blocking the lumen. If the vessel branches at this point, the emboli may be forced into a dendritic or stellate form. In the capillaries the fat is seen in the form of small ovoid or spherical emboli which may be so numerous that the alveolar walls are outlined as if by strings of beads. As noted by Wegelin,⁵⁵ all parts of the lung are about equally involved.

As a rule, the capillaries contain a large number of fat emboli only in persons who have had severe asphyxial symptoms during life. After an injury the fat first lodges in the arterioles, where it stays unless the pulmonary circulation is impeded by the embolism. When this occurs, the fat globules in the arterioles are forced into the capillary network and are broken up into smaller globules in the process. Not infrequently a small amount of the fat is forced further on into the systemic circulation, so that in cases of severe pulmonary involvement isolated emboli can be found in the finer vessels of the kidney, myocardium and cerebral cortex.

Aside from the embolism in the vessels the lungs show fluid in the alveoli, in which are red blood cells, leukocytes, large spherical cells and the like. In some instances the exudate may become frankly that of a bronchopneumonia. In rare instances fibrinous thrombi may form ante mortem in some of the smaller arteries as a result of the stasis in the pulmonary circulation.

The presence in the alveoli of large spherical cells containing fat granules is noted often and similar cells are found in the sputum during life. Elting and Martin⁵⁶ regarded this as an important diagnostic sign. In the absence of fat embolism, however, similar cells have been found in the lungs in various toxic conditions. For this reason, their presence cannot be considered pathognomonic.

55. Wegelin, C.: *Schweiz. med. Wchnschr.* 4:133 (Feb. 8) 1923.

56. Elting, A. W., and Martin, C. E.: *Ann. Surg.* 82:336 (Sept.) 1925.

Several examples of pulmonary fat embolism, of severe enough grade to be clinically important, were found in the necropsy material. They could be divided arbitrarily into two categories: (1) cases in which the fat embolism in the lungs was severe enough to contribute to the death of the patient, if associated with some other morbid condition, and (2) cases in which the grade of fat embolism was so marked that it caused death by itself.

Unfortunately, in all instances an adequate clinical history was not obtainable, but the postmortem observations indicated the true condition sufficiently well. Category 1 was represented by three cases.

CASE 1.—A white woman, aged 70, sustained a compound fracture of the left tibia and fibula in an automobile accident. She survived the injury four days. At necropsy, an infected compound fracture of the left leg was found, and a few of the ribs were fractured. Signs indicated that the chief cause of death was septic poisoning. However, there were numerous fat emboli in the arterioles and capillaries of the lungs and a few in the cerebral cortex and glomeruli of the kidneys. The fat embolism in all probability contributed to the fatal result through its effect on the pulmonary circulation.

CASE 2.—A white man, aged 75, was struck by an automobile and suffered a fracture of the left tibia and fibula, the left clavicle and eight ribs on the left side. He died about twenty-four hours after the injury. A clinical history of his symptoms was not obtainable. Necropsy revealed all the signs of a marked general arteriosclerosis and, in particular, a marked fibrosis of the left ventricle. The lungs were congested and edematous. Microscopic examination showed numerous fat emboli in the arterioles and capillaries of the lung, and a few in the cerebral cortex and the glomeruli of the kidneys. It was obvious that the embolism was severe enough to embarrass the circulation already damaged by arteriosclerotic processes.

CASE 3.—A man, aged 39, was struck in the abdomen by an automobile. He entered the hospital complaining of rigidity and tenderness in the upper left quadrant. The symptoms strongly suggested an internal abdominal injury, so a laparotomy was performed under ether anesthesia about two hours after admission. A contusion of the left rectus abdominalis was noted, but the internal organs were intact and the peritoneal cavity was normal. After the operation, a hypostatic pneumonia developed and the patient died of this complication two and a half days after he sustained the trauma.

Necropsy disclosed the contusion of the abdominal wall, the laparotomy wound and a severe hypostatic pneumonia of both lungs. The skin and tissues were slightly icteric and more or less dehydrated. It was evident that the patient was suffering from considerable toxemia. Microscopic examination revealed numerous fat emboli in the arterioles and capillaries of the lung, but there were none present in the brain, heart or kidneys. There were indications, however, that the right side of the heart had been somewhat embarrassed by the embolism in the lungs, for in places the white matter of the cerebral cortex showed red dots, the size of a pinhead and circular in outline, which on section were found to be engorged veins. They were produced by back pressure in the venous system, combined with the toxemia from the pneumonia, which had the effect of causing a marked distention of the vessels.

In all these cases the degree of fat embolism was about the same. Most of the arterioles were filled with fat globules, and here and there the walls of from two to four adjacent alveoli showed distinct rows of fat globules in the capillaries. It is possible that in itself the process might not have resulted fatally, but in combination with other pathologic conditions the embolism caused enough embarrassment of the pulmonary circulation to hasten the death of the patient.

Many investigators consider that fat embolism not infrequently complicates other conditions to produce death; in general, this is the view expressed by Payr,⁵⁴ Groendahl³⁴ and Frauendorfer.¹¹ Payr,¹³ who investigated fat embolism after orthopedic manipulations, was of the opinion that the fatal result was attributable to the fat emboli acting in conjunction with status lymphaticus. Similarly, in the study of traumatic shock, Gold and Loeffler⁵⁷ reached the conclusion that the chief rôle of fat embolism was to increase the deleterious effects primarily attributable to the shock.

The second type of pulmonary fat embolism comprised those cases in which the process was so marked that it was capable of causing death.

CASE 4.—This case was described previously.⁵⁸ A man, aged 62, was struck by an automobile and sustained fractures of the right femur, right tibia and right fibula. He died thirty-six hours later in an asthmatic attack.

At necropsy, there was a moderate degree of coronary arteriosclerosis, chronic nephritis, senile atrophy of the brain and hypertrophy of the prostate. The lungs were large and edematous. Microscopic examination disclosed a marked capillary fat embolism of the alveolar walls, to such a degree that the alveoli in places were practically outlined by fat droplets. A few fat emboli were found in the brain, kidneys and heart muscle, but not in sufficient number to produce a lesion.

CASE 5.—A white man, aged 45, was found in a hallway at the foot of the stairs. There was no history of a definite trauma, but on admission to the hospital the patient was in coma, was deeply alcoholic and showed lacerations of the scalp, a fracture of the left fibula and a luxation of the inner end of the left clavicle. For the first ten hours after admission he was irrational but recovered consciousness sufficiently to tell his name and address. At this time it was noted that his respirations became more difficult and rapid, and his pulse rate increased steadily up to the time of his death, thirty-one hours after admission.

Necropsy disclosed a well developed adult male with a number of injuries. The left fibula was broken in two places, and the internal malleolus of the left tibia was broken across. There was a fracture of the sternum and of ribs 2, 3, 4, 5 and 6 on the left side anteriorly. These fractures were simple. There was a luxation of the inner end of the left clavicle. In addition there was a subcutaneous separation of the skin in the right popliteal space from the muscles through the fatty layer over an area 3 by 4 inches (7.6 by 10.1 cm.). The skull showed a small linear fracture posteriorly, but the brain was not lacerated.

57. Gold, E., and Loeffler, E.: *Ztschr. f. d. ges. exper. Med.* 38:155, 1923.

58. Vance, B. M.: *Fatal Fat Embolism*, *Arch. Path.* 7:554 (March) 1929; *Proc. New York Path. Soc.*, Dec. 15, 1928.

The internal organs showed the lungs to be heavy and edematous, with areas of atelectasis posteriorly, and a small patch of pneumonia in the anterior part of the left upper lobe, about 1 inch (2.5 cm.) in diameter. The heart was large but normal. The foramen ovale was not patent. The stomach was distended with a large quantity of foul-smelling fluid, but the rest of the gastro-intestinal tract was normal. The other internal organs were practically normal.

On microscopic examination the lungs were filled with a large number of fat emboli which crowded the capillaries and arterioles to such an extent that numerous alveoli were outlined by the lines of globular emboli (fig. 1). Considerable

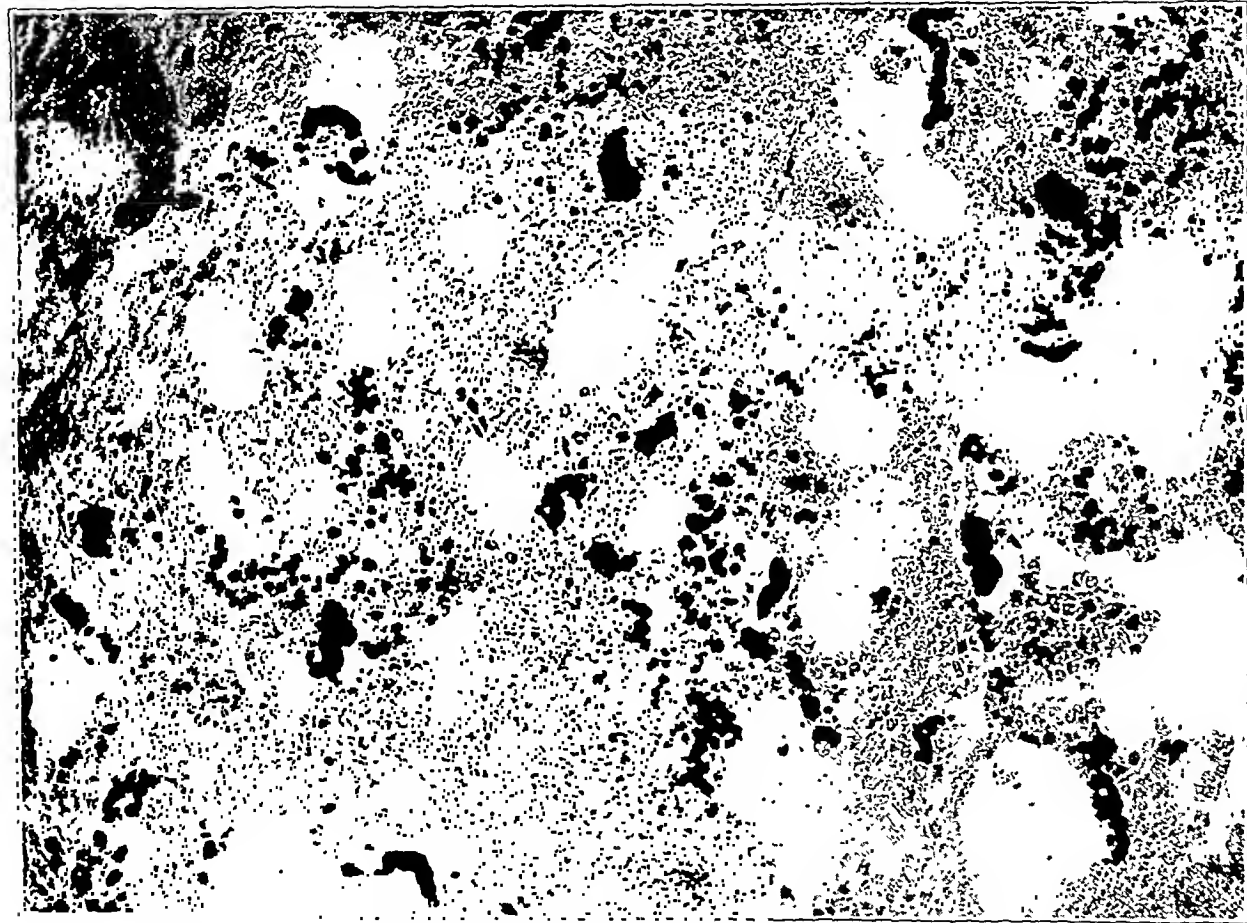


Fig. 1 (case 5).—Section of the lung in pulmonary fat embolism. Osmic acid stain.

edematous fluid was present in the alveolar lumen. A moderate number of emboli were found in the cerebral cortex, the myocardium and the glomeruli of the kidney.

In this case it is obvious that the embolism was the cause of death and that the pneumonia was so slight that it was merely a complicating and terminal factor.

SYSTEMIC OR CEREBRAL FAT EMBOLISM

In a few patients fat emboli may pass in large numbers from the pulmonary circulation into the arterial circulation, and hence be dis-

tributed to all the organs of the body, especially the brain, heart and kidneys. The most prominent symptoms are caused by the action of this process on the brain, and so the term cerebral fat embolism has been applied to the condition by Payr,⁵⁴ Groendahl³⁴ and others.

The fat is supposed to be transferred from the venous circulation to the arterial vessels in two ways:

1. It is transferred through some opening which enables the right side of the heart to communicate with the left side, which in most instances is the foramen ovale. According to Kaufmann,⁵⁹ the foramen is present in 33.33 per cent of all cases that come to necropsy, and is located in the interauricular septum. It can generally be demonstrated as a narrow slit, penetrating the septal wall obliquely, so that under normal conditions it is doubtful if blood ever passes through it from one circulation to the other. Certain investigators, including Naville and Fromberg⁶⁰ and Frauendorfer,¹¹ however, have expressed belief that in cases of fat embolism liquid fat may be forced from the right auricle through the foramen ovale into the left auricle. As Frauendorfer explained it, the blocking of the pulmonary vessels by the embolism raises the pressure in the pulmonary artery and the right side of the heart, and the foramen ovale is opened so that blood and oil pass into the left side of the heart. It cannot be proved, of course, that this method of transfer is impossible, but it has been shown that a cerebral fat embolism of a severe grade can occur in the absence of a patent foramen ovale or any other similar channel.

2. It is probable that the most important, if not the only, method of transference of the oil from the venous side to the arterial side is through the pulmonary capillaries into the pulmonary veins. As Groendahl³⁴ pointed out, the typical examples of this process are to be found in sthenic persons, whose right ventricle is strong enough to force the obstructing fat globules through the capillaries of the lung, which are relatively large and easily distensible. The process is greatly enhanced, according to Siegnund,⁵ by any subsequent trauma which may befall the patient. In his series of cases of fracture among the wounded in the battle field, the jarring inflicted on the patients in transporting them from one place to another undoubtedly forced the fat from the pulmonary capillaries into the arterial blood and caused systemic fat embolism.

After the fat has reached the left side of the heart, it is distributed immediately to the different parts of the body, blocks the arterioles and

59. Kaufmann, E.: *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, G. Reimer, 1911.

60. Naville, F., and Fromberg, C.: *Arch. de méd. expér. et d'anat. path.* **25**: 405 (July) 1913. Fromberg, C.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **26**: 23, 1913.

capillaries, and causes definite pathologic changes in the various organs. Because its arterial blood supply is extensive, the brain receives a large proportion of the fat emboli. These cause changes in the brain substance and evoke the clinical picture that Groendahl³⁴ and others have described under the name of cerebral fat embolism.

The symptoms of this complication can be divided into three stages which at times can be differentiated sharply but in other instances shade imperceptibly into one another:

(a) There is first the period between the trauma and the first appearance of symptoms, which averages from forty-eight to sixty hours in length, but which may vary from four hours to nine days. In this stage the patient is free from disturbing complications and is relatively comfortable.

(b) The soporific stage occurs next and is usually ushered in by premonitory signs, such as dyspnea, restlessness, precordial pains and increased pulse rate. Groendahl³⁴ suggested that this is the stage when the fat is passing through the pulmonary capillaries into the arterial blood and that it is probably referable to the difficulties experienced by the right side of the heart during this process. Shortly after, symptoms of cerebral origin occur, such as insomnia, loss of memory, disorientation and a slight delirium, which in alcoholic patients may become true delirium tremens. After a variable interval, the patient sinks into a stuporous condition and passes gradually into the last stage, that of coma.

(c) The coma becomes deeper and deeper, and is attended by various neurologic signs in many instances. The papillary and corneal reflexes gradually disappear. Signs of cortical irritation, such as muscular rigidity, clonic convulsions, tonic contractures and trismus, may present themselves. Paralytic involvement of muscular groups, especially around the arms and shoulders, occasionally occurs. As the coma grows deeper, there may be a general flaccidity of all muscles, followed by paralysis of the sphincters. From 24 to 100 hours after the onset of the coma, death occurs in profound unconsciousness, heralded at first by small rapid respirations, which later change to the Cheyne-Stokes type. As a rule, signs of cerebral compression are absent from the clinical picture.

The onset of coma and the fatal result are referable directly to the fat emboli which literally pervade all parts of the central nervous system, especially the brain. The fat entering the cerebral vessels is broken up into small emboli and is lodged in the precapillary and capillary vessels of the cortex and white matter. It is not known whether the brain is involved by a single invasion of emboli or whether separate invasions occur from time to time. In either event the blocking

of the vessels by the globules causes distinct lesions of the brain substance, which are grossly and microscopically evident.

Macroscopic examination of the brain, as recorded by Groendahl,⁵⁴ Gauss,¹ Melchior,⁶¹ Weimann⁶² and others, discloses a varying grade of congestion of the brain substance, with numerous small petechial hemorrhages pervading the white matter of the brain and cord, especially the region of the centrum ovale in the vault of the cerebrum. The hemorrhages are the size of a pinhead, are usually grouped in colonies of from four to twelve and literally pepper the brain substance. Weimann⁶² claimed that they may be so thick as to be almost confluent.

Under the microscope fat emboli can be demonstrated in arterioles and capillaries in all parts of the central nervous system including the cord, ganglions, membranes and choroid plexus. The most serious involvement takes place in the white and gray matter of the brain.

The gray matter is invaded the earliest and the most profusely by the emboli. Very few lesions can be demonstrated, however, as the capillary anastomoses are so extensive that the nutrition of the tissue is rarely impaired under normal conditions. The most that can be seen is the emboli filling the arterioles as sausage-shaped globules or as spherical bodies arranged in rows like beads. As Buerger⁶³ noted, it is only in brains already damaged by syphilis or by chronic alcoholism that definite lesions of the gray matter can be observed.

In the white matter the situation is different. The arterioles are end-vessels which branch in a dendritic fashion, and which communicate by scant capillary anastomoses. The embolus obstructing such a vessel effectively impairs the nutrition of the tissue that it supplies, and degenerative changes occur. Some of these changes result in petechial hemorrhages, and others appear as peculiar anemic areas of necrosis termed "rarefied areas."

The majority of investigators believe that the hemorrhages are minute infarcts caused by fat emboli in the cerebral arterioles, though there are differences of opinion concerning the exact method of production. Frauendorfer¹¹ attributed the hemorrhages to rhexis of the vessel wall by pressure from the embolus. Groendahl believed that the blood is extravasated from the capillaries in the healthy tissue surrounding the area of necrosis. Weimann⁶² remarked, however, that it is not possible to tell just how much these various mechanisms may operate in every instance.

61. Melchior: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **38**:178, 1924-1925.

62. Weimann, Waldemar: *Deutsche Ztschr. f. d. ges. gerichtl. Med.* **13**:95 (Feb.) 1929.

63. Buerger, L.: *Med. Klin.* **11**:996 (Sept. 5) 1915.

Toenniessen⁶⁴ was the only writer to offer another explanation for the production of the petechial hemorrhages. He said that they are not the result of emboli in the cerebral vessels, but are referable to a marked pulmonary fat embolism which causes back pressure in the superior vena cava and consequent rupture of the minute blood vessels in the brain. It is probable that a few hemorrhages may be produced in this fashion, but in most instances this mechanism is not important.

On microscopic examination a cross-section of the early stages of the petechial hemorrhages shows a fat embolus filling a small arteriole, while around the vessel is a circular zone of necrotic brain tissue and around this a circular zone of extravasated red blood cells. From this appearance the name of ring hemorrhage has been applied to the lesion. Longitudinal sections of such a vessel show that the part of the arteriole that is distal to the embolus is capped by a conical covering of necrotic tissue surrounded, in turn, by the layer of red blood cells. The lesion is, in fact, a microscopic hemorrhagic infarct, and the extravasated blood is probably derived from the capillaries immediately surrounding the necrotic area, as Groendahl³⁴ has already mentioned.

Later the processes of inflammation and repair occur. Inflammatory cells like leukocytes and lymphocytes invade the necrotic tissue; the ganglion cells and axis cylinders disintegrate; hyaline bodies, amyloid bodies and hemosiderin granules make their appearance. Finally large cells of glial origin appear. The end-result of the process is the removal of the embolus and the formation of a scar. This was observed in experimental animals by Paul and Windholz⁶⁵ but it has not been fully described in human tissues.

In some instances the fat emboli in arterioles supplying a portion of the brain substance cause areas of necrosis without hemorrhage, which have been termed "rarefied areas." As a rule, they are minute, irregularly ovoid and, in the early stages, translucent and meshlike. The blood vessels in the immediate surroundings are filled with fat emboli. Apparently the process is a sudden and intense destruction of the medullary sheaths due to anemic necrosis, with preservation of the axis cylinders, while at the same time lymphatic fluid pours in from the surrounding tissues and widens the meshes. Later the process of repair sets in and glial cells tend to fill in the spaces. The absence of a hemorrhagic zone around this lesion is probably due to the fact that the capillaries in the surrounding healthy tissue are blocked off from the necrotic zone by the embolism and so blood is not extravasated. The lesion is in reality a minute anemic infarct of the brain.

64. Toenniessen, Otto: *München. med. Wehnschr.* **68**:1280 (Oct. 7) 1921.

65. Paul, Fritz; and Windholz, Franz: *Mitt. a. d. Grenzgeb. d. Med. u. Chir* **38**:614, 1924-1925.

Kidney.—The kidneys are involved almost invariably in cases of systemic fat embolism though they fail to show characteristic changes on microscopic examination. The principal lesion consists of large snakelike or pretzel-like emboli filling the capillary coils of the glomeruli. They occur less often in the vasa afferentia.

Other changes occur less consistently, and there is considerable doubt whether they are due to the emboli or to other processes. Occasionally fine fatty granules fill the cytoplasm of the epithelial cells of the convoluted tubules; these were attributed by Groendahl³⁴ to the curtailment of the blood supply by the fat plug in the glomeruli, and by Scriba⁴³ and Buerger⁶³ to toxic action initiated by the embolism. Buerger described small hemorrhages in the kidney substance and thrombus formation and necrosis around the embolus which he also attributed to the action of toxic products set free by saponification of the embolus.

Several investigators have expressed the belief that the presence of fat emboli in the kidney will cause uremic symptoms and anuria. Busse⁹ described a case of anuria that was complete for about forty-eight hours prior to death. Paul and Windholz⁶⁵ claimed that in their case uremia, albuminuria, urinary casts and a gangrenous enteritis of uremic origin developed. Others, including Groendahl,³⁴ doubted that fat embolism can produce such extreme manifestations because the emboli do not involve all the glomeruli. The experiments of Paul and Windholz and of Flick and Traum⁶⁶ indicated, however, that a certain degree of interference with the excretory function of the kidneys can be caused by the glomerular lesions. It is probable that in a patient whose kidneys are already diseased, the embolic process may cause uremia or anuria to develop, though it might not have a like effect on comparatively normal organs.

Lipuria, or fat in the urine, has been described in many cases by Scriba⁴³ and others. There is considerable divergence of opinion concerning the way in which the fat is excreted. Scriba regarded it as a filtration into Bowman's capsule through the intact vessel wall. Ribbert⁶⁷ said that the fat ruptures the glomeruli and thus gains access to the tubules, or it appears as the result of secondary degeneration and destruction of the tubular epithelium. Some observers, including Scriba,⁴³ consider the excretion through the kidneys one of the most important ways of getting rid of the intravascular fat; others, including Groendahl,³⁴ regard it as a process of minor importance and claim that fat cannot be demonstrated in the lumen of the tubules in cases of fat embolism. At the present time, however, lipuria is held by some to be a certain diagnostic sign of fat embolism, even though

66. Flick, K., and Traum, E.: *Deutsche Ztschr. f. Chir.* 222:274, 1930.

67. Ribbert (footnote 10, first reference).

the details of the process are still a trifle obscure. Its true significance can be determined only by future investigations.

Heart.—In systemic fat embolism the heart is invaded rather frequently and on macroscopic examination shows numerous streaky hemorrhages, from 1 to 3 mm. in diameter, in the ventricular muscle. At times the larger hemorrhages contain a yellowish-white centrum in the midst of the dark red streak. Under the microscope the arterioles and capillaries are seen to be filled with sausage-shaped emboli, and on occasion the peculiar ladder-like anastomoses of the myocardial capillaries can be demonstrated.

The adjacent muscle fibers are peppered with minute fat granules and are smaller than the normal fibers. Numerous red blood cells surround the emboli and infiltrate between the fibers. The lesion is a true hemorrhagic infarct of minute size. Permanent scars due to this process have not been described, however.

When the emboli appear in large numbers the cardiac muscle is probably weakened, as Colley¹⁶ suggested, but it is difficult to estimate their influence on the clinical symptomatology. Similar lesions in the skeletal muscles have been described by Warthin.²⁴

Skin and Mucous Membranes.—The skin of the upper part of the chest, the shoulders and the anterior part of the neck are frequently peppered with small dark red petechial hemorrhages, the size of a pin head, and usually gathered in groups of from four to twelve, which make their appearance about the time the patient lapses into stupor. These changes are referable to a fat embolism of the arterioles of the dermis, which in some way causes an extravasation of red blood cells around the affected vessel. The process is comparable to similar lesions in the heart and brain. When the hemorrhages are discovered during life they are an excellent aid in diagnosis, as in the cases described by Groendahl³⁴ and others. After a lapse of several days they tend to disappear. Similar petechial hemorrhages have been noted on the conjunctivae by Busch³ and Frauendorfer,¹¹ on the soft palate by Wilke⁶⁸ and in the gastro-intestinal tract and bladder by Naville and Fromberg.⁶⁹ As a rule, these petechiae do not produce permanent lesions. Schridde⁷⁰ described multiple small erosions of the mucous membrane of the stomach, which he attributed to fat emboli.

Liver.—On macroscopic examination the liver does not show any noteworthy changes. Microscopic examination discloses fat emboli in the capillaries and occasionally fatty granules in adjacent parenchyma cells and Kupffer's star-shaped cells. Clinically there are no symptoms

68. Wilke: München. med. Wchnschr. **60**:1970 (Sept. 2) 1913.

69. Naville and Frömberg (footnote 60, first reference).

70. Schridde: Verhandl. d. deutsch. path. Gesellsch. **11**:234, 1907.

that can be referred to this embolism of the liver, though the experimental work of Paul and Windholz⁶⁵ indicated that the glycogen metabolism shows some disturbance.

The spleen shows fat emboli in the outer rim of the splenic follicle, but the parenchyma of the organ is not damaged, as a rule.

The suprarenals, pancreas and thyroid contain fat emboli, but aside from the presence of fat granules in the adjacent parenchyma cells and occasional extravasations of red blood cells, few other changes have been described.

In systemic fat embolism the lungs show the lesions that have already been described under pulmonary fat embolism.

Two examples of systemic fat embolism were encountered among the routine necropsies.

CASE 6.—A white woman, aged 65, was struck by an automobile; the shafts of the right femur, right radius and right ulna were fractured. She was admitted to a hospital in coma, and remained so until her death two days later. A more detailed history of her clinical course could not be obtained.

Necropsy disclosed the fractures of the extremities already mentioned, and in addition, lacerations of the left side of the forehead. There was also a short fracture of the left anterior fossa of the skull. The brain was not lacerated, but showed numerous petechial hemorrhages grouped in colonies of from four to ten, scattered throughout the white but not the gray matter.

The myocardium showed a moderate grade of brown atrophy and was permeated by numerous streaky hemorrhages, from 2 to 4 mm. in diameter. There was a small circular opening, 3 mm. in diameter, in the fossa ovalis allowing free communication between the right and left auricles.

The lungs were congested, well aerated and normal aside from a small amount of atelectasis posteriorly. The other organs were normal. Petechial hemorrhages could not be found on the skin.

Microscopic examination disclosed a widespread systemic fat embolism. As the histologic features were similar to those in case 7, the description will be given later.

CASE 7.—A strongly built white man, aged 65, was struck by an automobile and admitted to the hospital in coma. A severe contusion of the right eyelids, a Pott's fracture of the right fibula and compound comminuted fractures of the lower end of the left tibia and fibula were found. Blood was noted issuing from the nose and the left ear canal. A lumbar puncture revealed blood in the spinal fluid. A tentative diagnosis of fracture of the skull was made from these observations.

On admission to the hospital the blood pressure was 154 systolic and 88 diastolic. Six hours later it dropped to 94 systolic and 65 diastolic. An injury of the brain was suspected, but a satisfactory neurologic examination could not be made because of the condition of the patient. He remained in coma while in the hospital and died two days and eight hours after admission.

Necropsy disclosed a strongly built man, aged 65, who showed the external injuries already described. In addition there were numerous petechial hemorrhages of the front part of the chest, neck and shoulders; these occurred in groups of from four to twelve. Similar hemorrhages were noted in the conjunctivae.

The skull showed a linear fracture in the left middle fossa which, however, was not attended by a laceration of the brain or any other intracranial injury. There were numerous petechial hemorrhages, the size of a pinhead, scattered in groups through the white matter of the brain, especially in the vertex of the cerebral hemisphere. There was none present in the gray matter. The cerebral arteries were slightly sclerotic.

The heart showed a slight hypertrophy and coronary arteriosclerosis. The myocardium was permeated by ovoid and flamelike hemorrhages, from 1 to 3 mm. in diameter. It is significant that a foramen ovale or other communication between the right and left sides of the heart was not present.

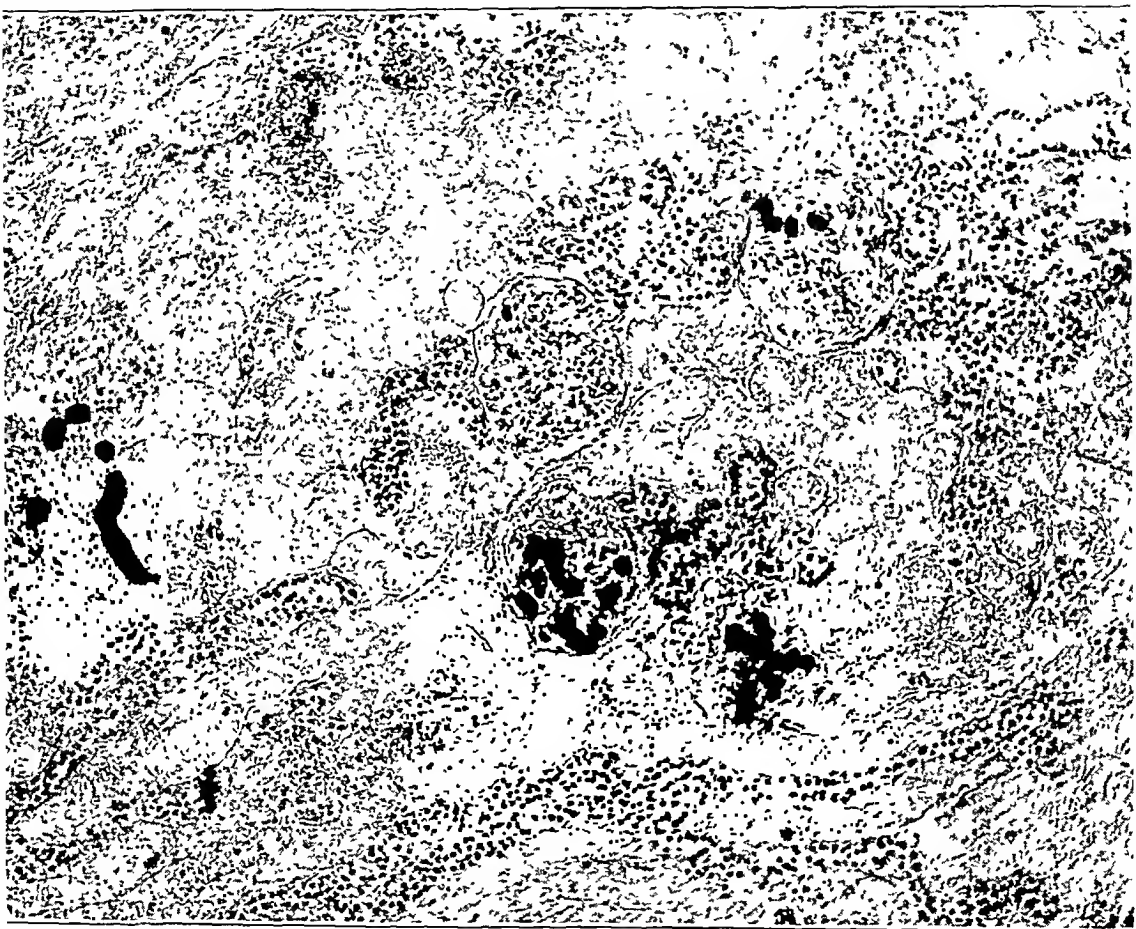


Fig. 2 (case 7).—Fat emboli in the glomeruli of the kidney. Osmic acid stain.

The lungs were heavy and voluminous but showed mainly congestion and edema.

The kidneys were normal, aside from a moderate grade of arteriosclerotic change.

On microscopic examination a widespread fat embolism of the lungs, brain and other organs was disclosed. The arterioles and capillaries of the lungs were filled with numerous fat plugs, which outlined the alveoli in many places.

The kidneys showed the characteristic snakelike and pretzel-like emboli in the glomerular coils, but no other noteworthy changes (fig. 2).

The myocardium disclosed numerous ovoid fat emboli in the arterioles and even in the capillaries, showing anastomoses in places. There was fatty degeneration and atrophy of the fibers immediately adjacent to the emboli and also hemorrhage between the muscle fibers. Some of these areas of embolism and degeneration were large.

The lesions in the brain were the most characteristic. Numerous ring hemorrhages and areas of rarefaction were found in the white matter adjacent to the fat emboli. In the gray matter numerous emboli were present in the arterioles, but lesions of the brain tissue were noted only occasionally (figs. 3 and 4).

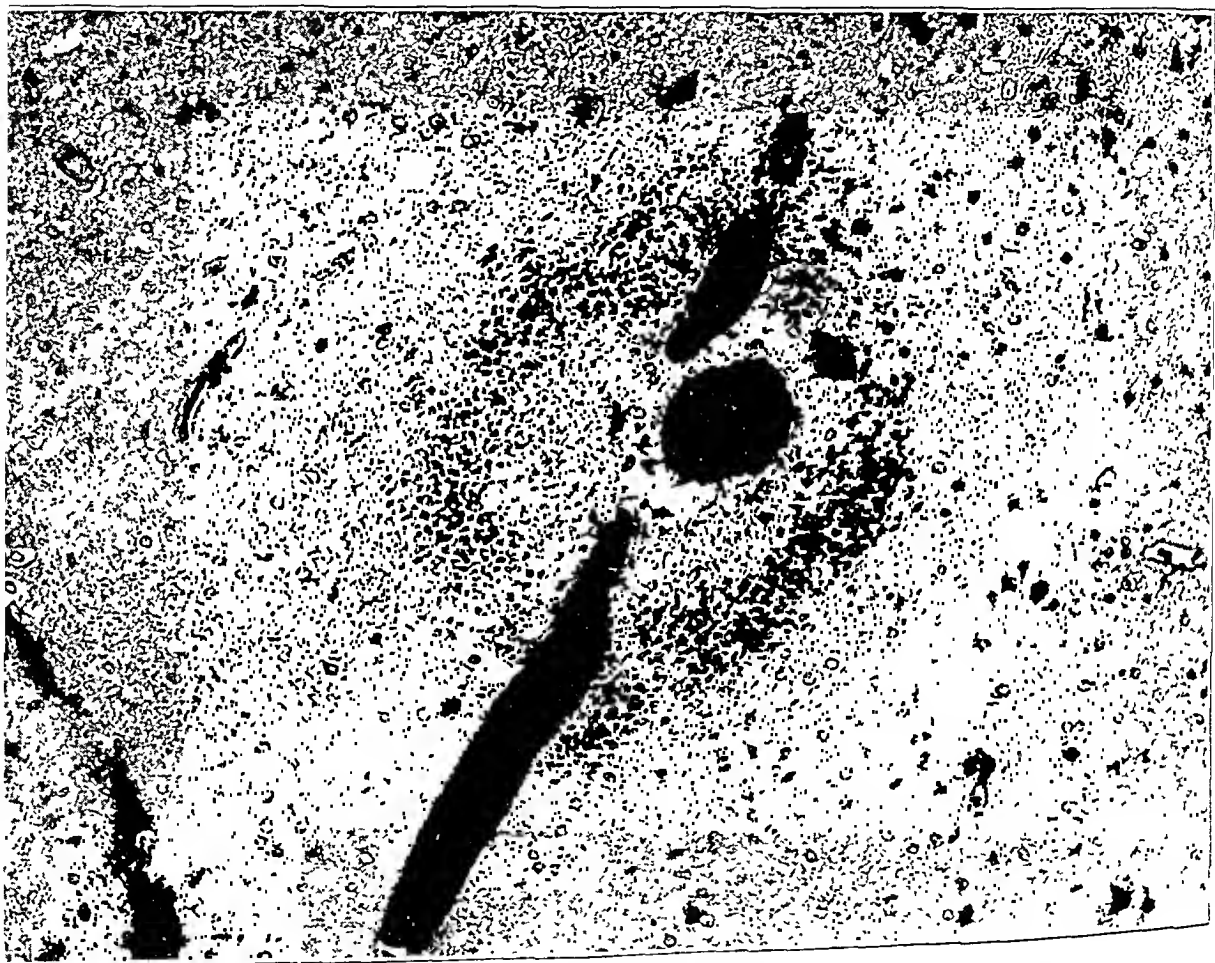


Fig. 3 (case 6).—Typical ring hemorrhage in brain, showing a fat embolus in an arteriole surrounded by a zone of necrotic brain tissue and red blood cells. Osmic acid stain.

These cases illustrate the difficulty of diagnosis whenever injuries to the head and fractures of the long bones are combined in the same patient. The fact that both patients were admitted to the hospital in coma and remained in coma as the result of the fractures of the skull obscured the typical clinical history of the cerebral fat embolism which developed later.

The absence of a patent foramen ovale or other communication between the right and left sides of the heart in case 7 is important in indicating that a systemic fat embolism can develop in the absence of any such opening.

Two cases described previously in a former report⁵⁸ illustrated the typical history of the cerebral fat embolism. One (case 8) was in a man, aged 25, who sustained a fracture of the right femur in an automobile

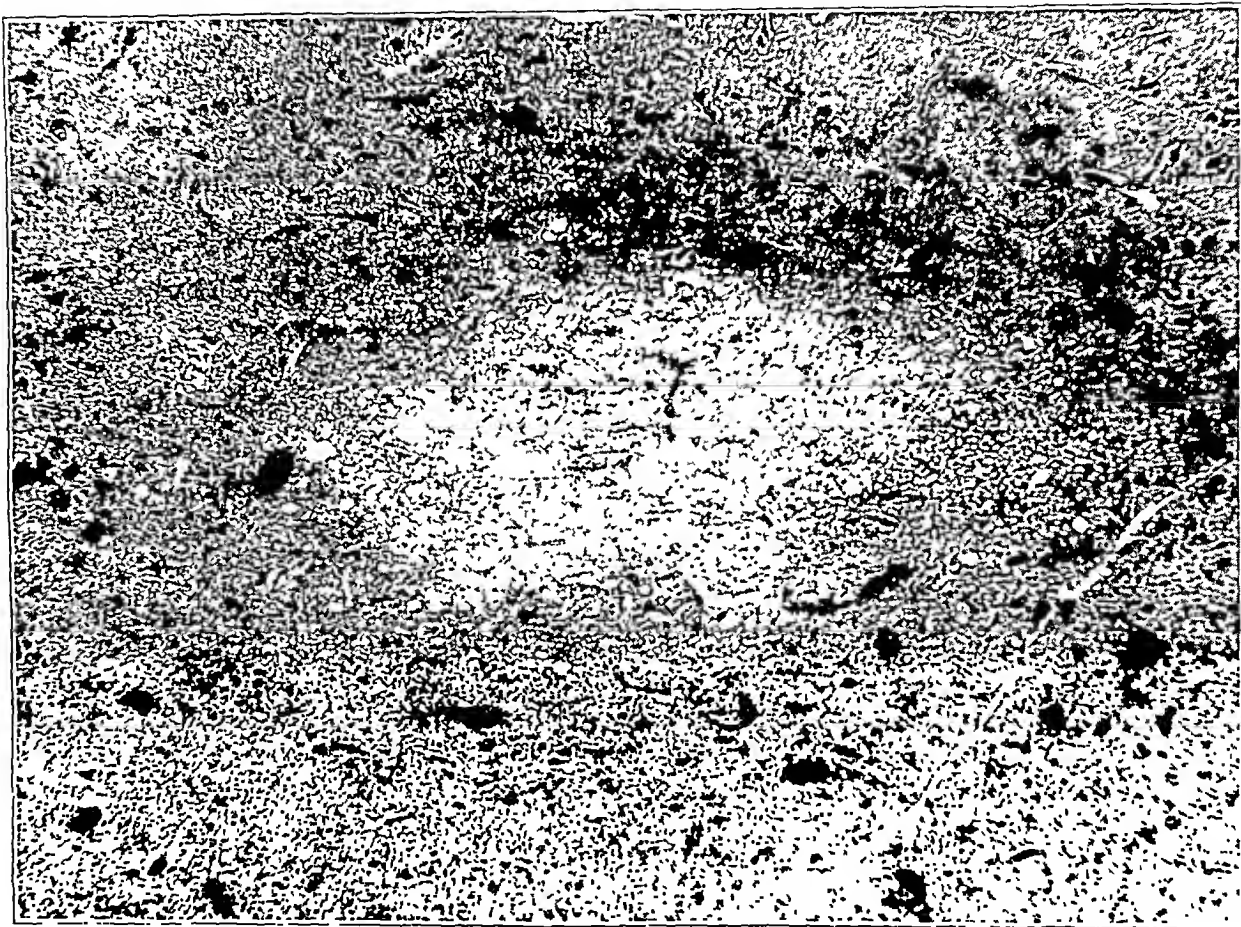


Fig. 4 (case 6).—Area of rarefaction in brain, with fat emboli in surrounding vessels. Osmic acid stain.

accident and lapsed gradually into coma about thirty hours after the injury. He died in coma six days and six hours following the trauma. In the other instance (case 9) a woman, aged 45, sustained a fracture of the right tibia and fibula in an automobile accident: two days later she lapsed into coma and died in coma four days later. In both cases petechial hemorrhages appeared on the skin of the upper part of the chest about the time that stupor developed, and they were still evident at the time of necropsy. Ring hemorrhages and areas of rarefaction were

present in the brain with numerous fat emboli in the vessels. These lesions showed the invasion of glial cells into the necrotic zones of brain tissue and attempts at repair (fig. 5). There were also fat emboli in the lungs, myocardium and kidneys which, however, were not obviously different from others already noted.

THE DIAGNOSIS AND TREATMENT OF FAT EMBOLISM

The majority of cases of fat embolism are so slight that they do not cause symptoms, or so severe that death results in a few days from

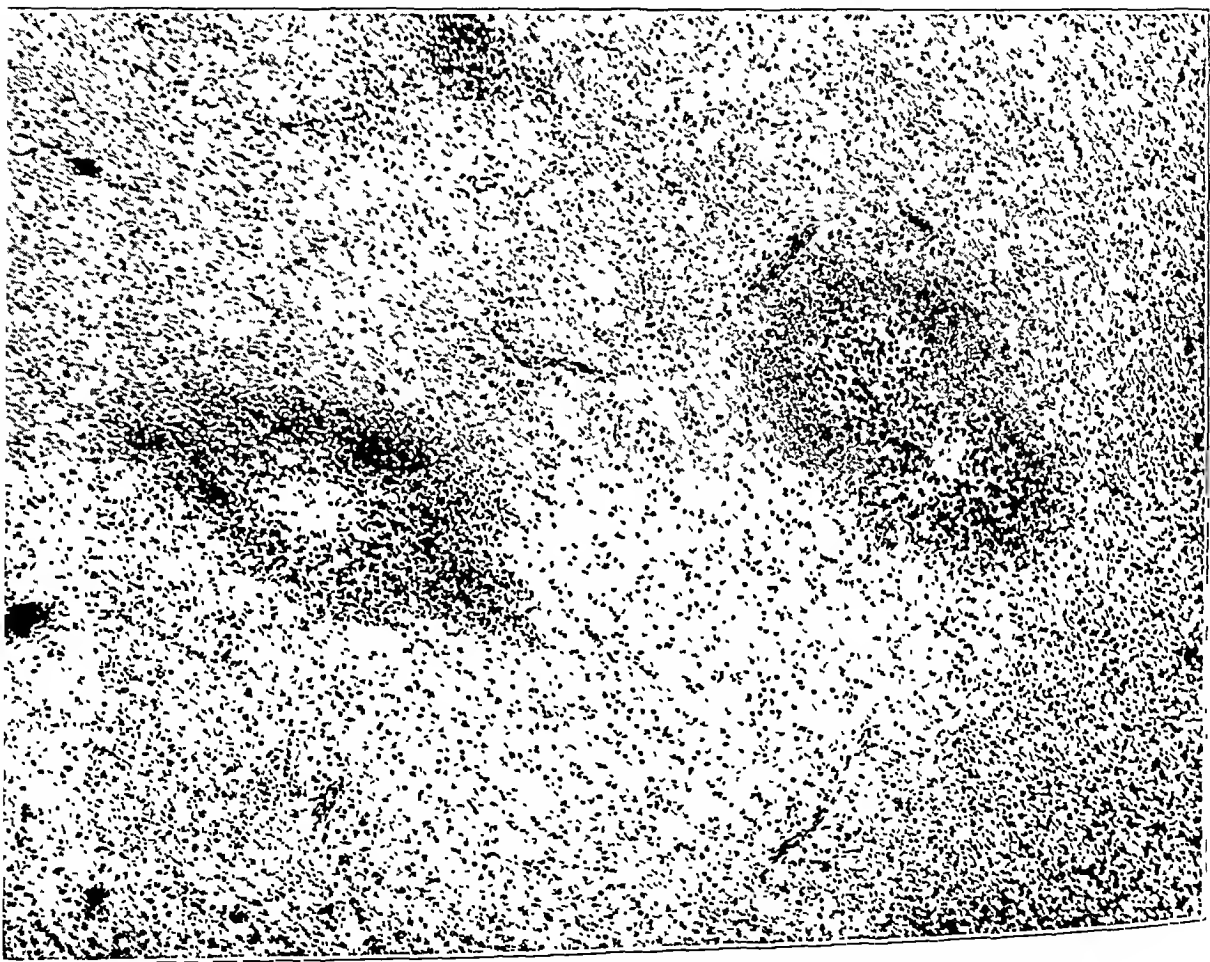


Fig. 5 (case 8).—Glial cells in an old ring hemorrhage. Hematoxylin and eosin stain.

involvement of the lungs or the brain. A few, however, have been reported in patients who after an injury gave a clinical picture of either the pulmonary or the cerebral form of this condition but who eventually recovered.

In two cases the diagnosis of pulmonary fat embolism was made. Field ⁷¹ described a case in which a patient who had suffered for several

71. Field, Merton: Fat Embolism from a Chronic Osteomyelitis, *J. A. M. A.* 59:2065 (Dec. 7) 1912.

years from chronic osteomyelitis of the leg, one day inflicted an insignificant trauma on the diseased bone; after this a sudden attack of dyspnea developed and gross fat appeared in the urine. The patient recovered and the diagnosis of fat embolism was made from the clinical picture. In the case of Koch,³¹ sterile human fat was injected into an old scar on the neck, and a few hours later the patient was seized with a severe but transient attack of shortness of breath. Koch attributed these symptoms to the fact that the fat was accidentally injected into a small vein and thus reached the blood vessels of the lungs. The diagnoses in both cases were probably correct, but of course there was no method by which they could be verified with certainty and the symptoms may have been due to other causes.

Other cases were described as examples of systemic fat embolism by Busse,⁹ Bernhardt,⁷² Wilms,⁷³ Benestadt⁷⁴ and Oppenheimer.⁷⁵ Each patient had sustained fractures of the long bones, and after an interval a slight stupor developed from which they recovered. In the cases of Busse⁹ and Wilms⁷³ the diagnosis was made on these symptoms alone. Bernhardt⁷² and Oppenheimer⁷⁵ claimed that they could detect the fat in the retinal arteries as ovoid globules, by use of the ophthalmoscope. The three cases of Benestadt⁷⁴ showed petechial hemorrhages in the skin of the shoulders and chest which gradually disappeared in a few days.

During life the diagnosis of fat embolism is justified only if there is a definite history of injury, and a characteristic clinical picture of either the pulmonary or the systemic type. Additional confirmatory signs are the presence of fat in the urine, the demonstration of fat emboli in the retinal vessels by the ophthalmoscope, and the appearance of the characteristic petechial hemorrhages in the skin of the upper part of the chest and shoulders. The discovery of large circular cells containing fat granules in the sputum, as noted by Elting and Martin,⁵⁶ and in the spinal fluid, as noted by Buerger,⁶³ is not a valuable diagnostic indication as the same changes can occur in other conditions than fat embolism.

As a rule, fat embolism is rarely diagnosed from clinical signs and symptoms; it is most often discovered accidentally at necropsy.

The differential diagnosis between cerebral fat embolism and intracranial hemorrhage complicating fracture of the skull has presented itself in one instance at least. As reported by Tobler,⁷⁶ a man, aged 64,

72. Bernhardt, Friedrich: *München. med. Wchnschr.* **72**:1590 (Sept. 18) 1925.

73. Wilms: *Semaine méd.* **30**:138 (March 23) 1910.

74. Benestadt, George: *Deutsche Ztschr. f. Chir.* **112**:194 (Oct.) 1911.

75. Oppenheimer, H.: *Klin. Wchnschr.* **8**:24 (Jan. 1) 1929.

76. Tobler, J.: *Schweiz. med. Wchnschr.* **3**:452 (May 11) 1922.

was run over by a wagon and his right tibia fractured. On the second day after the accident he became stuporous and gradually lapsed into coma. A craniotomy was performed under the impression that he had a fracture of the skull with a complicating intracranial hemorrhage. No hemorrhage was found, and the patient died in deep coma on the fourth day after the trauma. Necropsy showed a marked cerebral fat embolism, but neither a fracture of the skull nor an intracranial hemorrhage.

It can readily be seen how the two conditions might be confused clinically under some circumstances. In a patient with a head injury and a fracture of a long bone of one of the extremities, a gradual lapse into coma might indicate an increasing intracranial hemorrhage, or a severe cerebral fat embolism. In typical cases the two would never be mistaken, as the intracranial hemorrhage is most often attended by signs of cerebral compression and definite neurologic signs referable to the site of the lesion. On the other hand, these syndromes are absent in cases of cerebral fat embolism, and lipuria, petechial hemorrhages of the upper part of the chest, and an ophthalmologic demonstration of the emboli in the retinal vessels may aid in establishing the diagnosis. Unfortunately, cases are not always typical, and often it is not possible to make the diagnosis during life.

The best treatment for fat embolism is to prevent its occurrence. In cases of fractures, effective immobilization of the broken bones is the most efficient means of lessening the absorption of the fat into the venous circulation. After the processes of repair have set in, the danger of this is past. In orthopedic cases, operations are performed by preference on patients whose marrow is cellular and not fatty, and an Esmarch bandage is used in an attempt to obviate the passage of an excessive amount of fat into the systemic veins from the operative site. Reiner⁷⁷ suggested that systematic tapping of the veins proximal to the fracture and distal to the Esmarch bandage would materially reduce the quantity of fat that reached the lungs, but there is no evidence that this method is at all effective.

Other therapeutic measures advised by different investigators are not of much practical value. The idea of Wegelin,⁵⁵ that an intravenous injection of sodium carbonate hastens removal of the emboli by saponification, does not promise to be effective. The theory of Wilms,⁷³ that drainage of the thoracic duct lessens the amount of fat embolism in the pulmonary vessels, is based on the false conception that fat is transported from the site of injury by the lymphatic vessels. As a therapeutic procedure it would be practically useless.

As a rule, when the fat has entered the blood stream, the result must be left to the natural defenses of the body and only symptomatic treatment can be applied.

77. Reiner: *München. med. Wchnschr.* 54:2004 (Oct. 1) 1907.

FAT EMBOLISM IN ANIMAL EXPERIMENTS

Much of the information concerning fat embolism has been acquired through experiments on animals, so that in order to gain an adequate conception of the subject it is necessary to review briefly the work in this field.

The early experiments were concerned mainly with the discovery that a viscous oil, like olive oil, when injected into the vein of an animal, produced death in a few minutes from asphyxia and edema of the lungs. Majendie⁷⁸ recorded the results of such an investigation about 1832. Over twenty years later Virchow⁷⁹ repeated the same experiment and, in addition demonstrated typical fat emboli in the pulmonary arterioles and capillaries, which he believed were responsible for the death of the animal.

Busch⁸ contributed an important addition to the general knowledge of the subject when he demonstrated that injuries to the adipose tissue in the skeleton resulted in a definite fat embolism in the lungs. He made a trephine opening in the tibia of a rabbit, traumatized the fatty marrow of the shaft with a sound and produced characteristic fat emboli in the pulmonary vessels. He also showed that if olive oil colored by cinnabar was injected through such a trephine opening into the medullary cavity of the tibia, three significant phenomena were noted: 1. The haversian canals of the bone into which the injection was made were stained heavily by the cinnabar, indicating that the colored olive oil had been absorbed into the haversian veins. 2. Numerous cinnabar-colored fat emboli were found in the lungs; this was additional evidence that they were derived from the fat in the bone marrow. 3. If the inferior vena cava was canalized just prior to the injection, cinnabar-stained oil globules would flow from the canalized vein immediately after the injection; this pointed to the fact that the absorption of the fat from the bone was rapid and that its transportation to the lungs was swift.

Much more recently the experiments of Fritzsche,⁸⁰ Schultze,¹² and Caldwell and Huber⁸¹ furnished additional verification that fat is rapidly absorbed from a fracture of the shafts of the long bones. Schultze fractured the tibia of his animals and then canalized the main venous trunk of that extremity. The primary fracture caused only a few droplets of fat to pass through the cannula, but any further trauma to the area of injury, such as light blows, movement of the bones or a sudden ecchymosis in the affected part, caused a large number of oil

78. Majendie, quoted by Scriba (footnote 43).

79. Virchow, Rudolph: *Virchows Arch. f. path. Anat.* **5**:308, 1853.

80. Fritzsche, E.: *Deutsche Ztschr. f. Chir.* **107**:456, 1910.

81. Caldwell, George T., and Huber, Harry L.: *Surg. Gynec. Obst.* **25**:650 (Dec.) 1917.

globules to enter the vein. He believed that the natural aspirating force of the torn haversian veins allowed the fat to gain entrance to the circulation, and that a rise of pressure in the area of fracture from hemorrhage, muscular spasms and the like would serve to increase the amount of fat absorbed to a dangerous degree. His experiments confirmed and supplemented the observations of Siegmund⁵ and Sutton⁶ on clinical cases.

Caldwell and Huber⁸¹ also produced pulmonary fat embolism by fracturing the tibia of rabbits. They claimed that if an Esmarch bandage was bound around the extremity proximal to the fracture and retained in position for two hours, the number of the emboli in the lungs would be much less than if the Esmarch bandage was not used. These observers explained their results by the fact that the two hour application of the bandage prevented a large absorption of fat until the processes of repair had closed the ruptured veins at the site of fracture.

The experiment of Ribbert⁸² seemed to indicate that fat embolism could be produced by trauma to the skeleton without actual fracture of the bones. He anesthetized a rabbit, struck the shaft of the tibia repeated light blows with a rod and later demonstrated fat emboli in the lungs. He did not describe any lesions in the bones or bone marrow, but attributed his results to the jarring force that he inflicted on the bone with the rod. Fritzsche⁸⁰ and Schultze¹² duplicated this experiment, and considered that the emboli could be caused in this manner. In fact, Fritzsche claimed that a slight grade of fat embolism is found normally in rabbits because of the propensity of the animals to thrash around in their cages. Similarly, McKibben⁸³ described fat embolism in normal cats. Schultze offered the explanation that the jarring of the bones tears small veins and ruptures small groups of fat cells at their attachment to the firm bony trabeculae, with the production of numerous minute hemorrhages in the bone marrow and a consequent rise of intra-osseous pressure. The mechanism for absorption of fat into the blood is thus provided and an embolism results.

A few investigators have believed that a lipemic condition of the blood can be a potent etiologic factor in the production of fat embolism. In lipemia, such as occurs during digestion, fat is present in the blood in the form of an emulsion so finely divided that it passes readily through the finer capillaries and, under normal conditions, rarely coalesces into globules large enough to cause vascular obstruction. Wuttig⁸⁴ claimed, however, that he produced pulmonary fat emboli in rabbits by causing lipemia from the excessive ingestion of cod liver oil. Similarly,

82. Ribbert (footnote 10, first reference).

83. McKibben, P. S.: *Am. J. Physiol.* **48**:331 (April) 1919.

84. Wuttig, H.: *Zieglers Beitr. z. path. Anat.* **37**:378, 1905.

Lehman and Moore⁸⁵ produced lipemia in dogs by feeding them cream, and then gave the animals ether, either intravenously or by inhalation. On postmortem examination fat emboli were found in the lungs in considerable numbers, while control animals whose blood was not lipemic did not show analogous changes. They believed that the ether acted as a deemulsifying agent by precipitating fat from the blood serum in globules large enough to plug the vessels.

Markowitz and Mann,⁸⁶ in their experiments on dogs, claimed that they produced histologic pictures resembling fat embolism in the lungs by the intravenous injection of finely divided fat emulsions. No explanation was given for the precipitation of the fat from this emulsified form into the larger globules in the blood.

At present it is too early to speak with any authority on the possibility of fat emboli arising from lipemia, but it is not probable that this condition is an important etiologic factor in human beings.

The transportation of the liquid fat from the site of injury to the pulmonary arterioles and capillaries is primarily through the venous circulation by the direct route, as the experiments of Busch³ and Schultze¹² have indicated. Some investigators, among whom are Busch, Wiener,⁸⁷ Riedel⁸⁸ and Fritzsche⁸⁰ have suggested that some of the fat is absorbed by torn lymphatic vessels and carried to the thoracic duct and eventually discharged into the venous circulation. After a lapse of twenty-four hours, a severe pulmonary fat embolism will be caused, according to Fritzsche. This investigator claimed that in his experiments on rabbits and dogs, ligation of the venous trunks draining the extremity on which a fracture had been inflicted could not keep the emboli from the pulmonary vessels, but that ligation of the thoracic duct inhibited their occurrence. Fritzsche's theory was that fat so absorbed had the power to pass unchanged through the lymph nodes in its route to the thoracic duct.

In recent years, the evidence is that very little fat is absorbed by the lymphatics at the site of injury, and that it is subjected to lytic changes in its progress through the adjacent lymph nodes. The experiments recorded by Wegelin⁵⁵ showed that olive oil injected into rabbits subcutaneously, intrapleurally and intraperitoneally gives rise to a few emboli in the lungs, and that most of the oil is found in the nearest lymph nodes in a state of saponification. According to Wegelin, the lymphatic tissues are strongly lipolytic, and fat is not likely to pass through them intact. In any event, it is dubious that liquid fat in

85. Lehman, E. P., and Moore, R. M.: Fat Embolism Including Experimental Production Without Trauma, *Arch. Surg.* **14**:621 (March) 1927.

86. Markowitz, Cecile; and Mann, F. C.: *Am. J. Physiol.* **73**:521 (June) 1930.

87. Wiener, M.: *Arch. f. exper. Path. u. Pharmacol.* **11**:275 (Sept. 3) 1879.

88. Riedel, B.: *Deutsche Ztschr. f. Chir.* **8**:571, 1877.

appreciable amount is conveyed from the injured area by the lymphatic vessels, and it is certain that the venous circulation is the only important channel in the production of the pulmonary form of embolism.

In its passage through the pulmonary arteries or other vessels the fat tends to break up into smaller and smaller globules as the emboli reach the finer and finer ramifications. As Fuchsig⁸⁹ noted in a fat embolism induced in the mesentery of the frog, the emboli divide into smaller globules which enter the capillary network in single file. Investigation of the lungs microscopically suggests that some such process takes place here. Apparently the distribution of the fat throughout the lungs is uniform for the most part. The theory of Kretz⁹⁰ that fat emboli entering the blood through tributaries of the superior vena cava involve mainly the upper lobes and that emboli entering in tributaries of the inferior vena cava involve mostly the lower lobes is not considered tenable. Wegelin⁹¹ noted that in any one case of fat embolism all parts of the lungs show practically the same proportion of emboli.

The effect of fat embolism on the organism has been the subject of much experimental study. It is evident from the results recorded that many factors influence the reaction of the animal to the injected mass. If it is given rapidly in large amounts into the jugular vein, as was recorded in the experiments of Virchow,⁷⁹ death occurs in a few minutes from asphyxia. If, however, the oil is injected slowly into a smaller venous trunk, larger quantities can be given before the animal shows signs of respiratory distress, as Wegelin mentioned. Paul and Windholz⁹² declared that by injecting large intravenous doses of oil in carefully graduated amounts at selected intervals they were able to create a tolerance for fat embolism in their animals. One that had been carefully prepared in this fashion could withstand comfortably the injection of an amount of oil sufficient to cause the death of an animal not similarly treated.

One effect of oil injected intravenously is to lower blood pressure, as was made manifest in the work of Simonds,⁹¹ Wiggers⁹² and Porter.⁹³ The widespread embolism obstructs the passage of blood through the pulmonary circulation into the systemic circulation, reduces the volume of fluid in the arterial trunks, and seriously interferes with the strength of the heart beat because of the interference with oxygenation in the pulmonary vessels. The arterial pressure conse-

89. Fuchsig, Ernst: *Ztschr. f. exper. Path. u. Therap.* **7**:702, 1910.

90. Kretz, quoted by Wegelin (footnote 55).

91. Simonds, J. P.: A Study of Low Blood Pressures Associated with Peptone Shock and Experimental Fat Embolism, *J. A. M. A.* **69**:883 (Sept. 15) 1917; *J. Exper. Med.* **27**:539 (May 1) 1918.

92. Wiggers, Carl B.: Circulatory Failure, *J. A. M. A.* **70**:508 (Feb. 23) 1918.

93. Porter, W. T.: *Boston M. & S. J.* **180**:531 (May 8) 1919.

quently decreases in a manner suggestive of shock induced by trauma. In fact, the similarity between the two conditions in this respect inspired the three investigators mentioned to see what connection might exist between traumatic shock and fat embolism.

As described by Cannon,⁹⁴ traumatic shock occurs shortly after severe wounds and is manifested by a general collapse of the organism, with lowered blood pressure, a rapid weak pulse and respirations, a low temperature, increased viscosity of the blood, signs of acidosis and similar symptoms, often severe enough to result in death. All these symptoms are referable to a stagnation and retention of the blood in the capillary bed of the body and an inability of the circulatory mechanism to force the blood properly through the vessels and oxygenate it sufficiently. The end-result is therefore a deficient interchange of oxygen, not only in the lungs but also in various organs elsewhere, with consequent damage to the injured person. It is evident that traumatic shock is composed of a number of different phenomena and that the knowledge of its etiology is as yet incomplete. From the results of observations and experiments, it seems probable that shock is a condition totally distinct from fat embolism, but that in occasional instances many of the symptoms referable to shock may be the result of an association with the latter condition.

The experiments of Gold and Loeffler⁵⁷ indicated the effects of an artificially induced fat embolism on an artificially induced traumatic shock in cats. Their cats were separated into two series: (1) normal animals used as controls, and (2) cats in which shock was produced either by traumatizing the intestines or by compressing the inferior vena cava near the liver. Liquid fat was injected intravenously into both series of animals. The control animals showed merely signs of a pulmonary fat embolism, with asphyxia, dyspnea and a slight decrease in blood pressure. The cats shocked by trauma exhibited a low blood pressure before the injection of oil, but if kept undisturbed usually returned to a normal state. The intravenous injection of oil in an amount that would scarcely affect a control animal had a deleterious effect on the shocked animal, for the blood pressure remained low and the symptoms of shock were unduly prolonged. Gold and Loeffler believed that fat embolism was distinct from traumatic shock but that it often occurred in association with the latter condition and merely enhanced the symptoms of vascular collapse already present.

The experiments of Scriba,⁴³ Reuter,⁹⁵ Kojo,⁹⁶ and Paul and Windholz⁶⁵ proved that fat injected into a systemic vein could pass through

94. Cannon, W. B.: A Consideration of the Nature of Wound Shock, *J. A. M. A.* **70**:611 (March 2) 1918.

95. Reuter, Wolfgang: *Frankfurt. Ztschr. f. Path.* **17**:205, 1915.

96. Kojo, quoted by Wegelin (footnote 55).

the pulmonary capillaries into the arterial circulation and be distributed to the different organs. A large portion of the emboli centered themselves in the brain. Scriba⁴³ was of the opinion that the lesions in the brain alone could produce sudden death. Fuchsig⁸⁹ and Porter⁹³ observed a case in which rapidly fatal collapse occurred when an artificial fat embolism of the medulla was produced. The latter was prone to attribute the lethal cases of wound shock to this condition. Others, including Reuter,⁹⁵ believed, on the contrary, that fat emboli cause comparatively little damage to the central nervous system. Reuter claimed that in his experiments olive oil injected into the carotid arteries of a rabbit passed the cerebral capillaries as well as the pulmonary capillaries, and eventually was found in the lungs. He regarded the lungs as a natural filter of liquid fat from the blood, and as capable of harboring large numbers of emboli without difficulty.

It was believed for a long time that liquid fat could be forced through the pulmonary capillaries into the arterial circulation and from the systemic capillaries back into the venous circulation. The process could be repeated until finally the fat was absorbed from the blood; the name given to it was cyclic fat embolism. It is possible that this condition has been approximated in animal experiments for, as Wegelin⁵⁵ pointed out, different oils have different viscosities; olive oil, for instance, is much less viscous than human fat and therefore more capable of passing through the capillaries. It is difficult to conceive, however, of any cyclic phenomena of this kind occurring in human pathology, especially in the fat embolism induced by trauma.

In recent years many oils of low viscosity have been given intravenously as a therapeutic measure. The use of chaulmoogra oil in leprosy is well known and it apparently can be given in this manner without ill effects. Fischer,⁴⁵ Leo⁹⁷ and Lepehne⁹⁸ experimented with intravenous injections of eucalyptol-menthol as an antiseptic agent in pulmonary tuberculosis and of camphor as a circulatory stimulant, but the solutions that they used appear to be irritative apart from whatever ill effects they may cause in the rôle of fat emboli.

Fat emboli have a definite action on the systemic organs and cause the lesions that have already been described. Recently the effect of the embolism on the blood chemistry of animals was studied by Paul and Windholz⁶⁵ and by Flick and Traum.⁶⁶ Paul and Windholz produced a nitrogen retention of a uremic type, and a marked hypoglycemia in the blood of rabbits by the intravenous injection of liquid human fat. They attributed these results to a widespread fat embolism of the kidney and liver, respectively. In addition, the same investigators

97. Leo, H.: *Deutsche med. Wchnschr.* 48:155 (Feb. 2) 1922.

98. Lepehne: *Klin. Wchnschr.* 1:670 (April 1) 1922.

described deposits of pigment in the spleen and fatty changes in the liver which they considered due to hemolytic and toxic products produced by saponification of the emboli.

Flick and Traum.⁶⁶ in a similar manner, injected dog fat intravenously into normal dogs and demonstrated that a nitrogen retention followed the embolism.

Schultze¹² suggested that in many instances fat absorbed from the fracture of a leg bone becomes adherent to the wall of the femoral vein and later undergoes saponification so that the intimal layer is irritated. A reactive inflammation is induced, and a bland thrombus may form in the vein. Just how far this process operates in thrombosis of the femoral veins following a fracture or other injury to the lower extremity is not well understood.

The elimination of fat emboli from the system has been estimated as occurring in from eight to fourteen days, according to Reuter.⁹⁵ Gauss¹ listed four ways in which the intravascular fat can be removed from the body: (1) excretion by the kidney, (2) disposal by the liver, (3) removal by phagocytic endothelial cells and (4) solution of the embolus by a lipase either in the blood or in the tissues.

The elimination of the fat by the kidney has already been discussed. As far as the liver is concerned, the experiment of Wuttig⁸⁴ showed that the parenchyma cells and Kupffer cells in the immediate vicinity of the embolus are filled with fat droplets. He believed that the organ has the power of absorbing the fat from the blood vessels. It is probable, however, that phagocytosis by endothelial cells, as noted by Beneke⁹⁹ and others, and saponification by lipases, as mentioned by Paul and Windholz⁶⁵ and by Wegelin,⁵⁵ are the two most important methods of removing the intravascular fat.

Lehman and McNattin¹⁰⁰ described this phagocytic process around the experimental fat emboli in the lungs of dogs that had received intravenous injections of cotton seed oil. At first, large endothelial and giant cells appeared around the fatty plug, and later areas of pneumonia and scar tissue nodules developed as an after-effect of the embolism.

Similar pictures have not been described in the experimental fat embolism of other organs, aside from a brief mention by Paul and Windholz of small glial scars in the brains of animals.

COMMENT AND SUMMARY

It is obvious that fat emboli frequently occur after trauma to fatty tissue, especially in the shafts of the long bones. In the majority of

99. Beneke, R.: *Zieglers Beitr. z. path. Anat.* **22**:343. 1897.

100. Lehman, E. P., and McNattin, R. F.: *South. M. J.* **22**:201 (March) 1929.

cases the grade of embolism is slight, indicating that the protective mechanisms of the organism work with sufficient efficiency to prevent the absorption of fat into the blood stream in any considerable amount. Severe and fatal cases of fat embolism are exceptional. Table 2, in which fifty-nine cases of fractures of the bones of the extremities are analyzed, shows about 75 per cent positive for fat emboli and 25 per cent negative. Only three cases, or approximately 5 per cent of the total number belonged to the fatal group.

An analysis of the material indicated that fat emboli could be demonstrated in the pulmonary arterioles a few minutes after a fracture. The transportation from the site of injury to the lungs was rapid. The emboli could be found rather consistently in the lungs during the first seven days after the trauma, but were discovered only occasionally after that period, as they were probably being removed from the circulation. The sections of the lungs and other organs were searched for evidences of phagocytosis or other signs of removal of the emboli; however, aside from finding large spherical cells with fatty granules near the impacted globule, the results were negative. As these same cells were occasionally present in toxic conditions not associated with fat embolism, little significance was attached to their appearance.

The positive results in the series of nontraumatic cases were only to be interpreted as an indication that in some way a small amount of fat had gained entrance to the circulation and formed emboli in the lungs. Probable explanations were that adipose tissue somewhere in the body had been slightly damaged from a convulsion or a fall, or that some oily substance like camphor had been injected into a subcutaneous vein by accident. In any event, the degree of the process was slight and not of any importance clinically or pathologically. Its chief significance lies in the implication that a slight grade of pulmonary fat embolism cannot be used as a positive confirmatory sign of trauma. Given a fracture of a bone in the leg in a person found dead under suspicious circumstances, unless other signs indicated that the violence was inflicted during life, a few fat emboli in the lungs would be useless as a criterion of intravital injury.

On the contrary, a severe grade of fat embolism, especially when some of the emboli have been forced from the pulmonary into the systemic circulation, is a reliable indication of intravital trauma, if a definite injury is present and if one can exclude the only other cause, the intravenous injection of an oily liquid in large amounts. As this last process is uncommon in human pathology, it can be ignored as a practical consideration.

Other alleged causes, such as burns, poisons, postmortem processes and lipemic conditions due to natural causes, are associated only with slight grades of fat embolism, and are not important.

It is also certain that severe fat embolism gives rise to two distinct clinical pictures associated with definite pathologic lesions: 1. The pulmonary type, which occurs in the first two days after the injury, is referable to a marked obstruction of the arterioles and capillaries of the lungs. The patients die as the result of asphyxial symptoms. 2. The emboli may pass through the pulmonary capillaries into the systemic circulation, and cause definite lesions in the brain, heart and other organs. In such instances, death occurs in from two to seven days from the involvement of the central nervous system; for this reason, this type is known as the cerebral type.

The clinical diagnosis of fat embolism is made only occasionally because the complication is rare and because the symptoms may be attributed to some other condition in the body. The asphyxial symptoms of the pulmonary form may be confused with the terminal symptoms of an associated chronic disease of the heart and lungs. This may occur all the more readily because a pulmonary embolism of moderate grade can aggravate lesions of this type.

The cerebral type is often overlooked, especially if an injury of the head is present, as the coma from the latter not only may obscure the typical clinical picture but, on occasion, may simulate it. This was seen in the case reported by Tobler,⁷⁶ in which the patient's lapse into unconsciousness was attributed to cerebral compression referable to a supposed epidural hemorrhage rather than to the widespread cerebral fat embolism that was actually present.

The diagnosis during life is not easy and can be made only if the possibility of fat embolism is kept in mind, and if the symptoms and signs that suggest it are not overlooked. For this purpose, hard and fast rules cannot be formulated, but much must be left to the native astuteness of the individual diagnostician.

NORMAL AND PATHOLOGIC REPAIR IN THE THYROID GLAND *

NATHAN A. WOMACK, M.D.

AND

WARREN H. COLE, M.D.

ST. LOUIS

In the large accumulation of studies referable to the thyroid gland, the vast majority are concerned chiefly with pathologic states, the most common being goiter with its various types and classifications. And yet not all goiters represent pathologic conditions. An enlargement of the thyroid gland is not an unusual event in the life of a person, especially in certain regions, and it often represents a physiologic response of the organ to certain stimuli. This gross change in the size of the gland is often associated with both chemical and microscopic changes. That increase in the activity of the thyroid gland is associated with an increase in the metabolism of the body is such a well known fact that it requires but little comment. This has been shown not only by an increase in the body's excretion of nitrogen, but by an increase in the consumption of oxygen. So definite is this that the level of the basal metabolism is often used as an index of thyroid activity. The cellular change seen in the gland may be both marked and varied. It may consist merely of a change in the size and shape of the cells with an increase in the mitochondria, or it may be so extensive, owing to hyperplasia and desquamation of the parenchyma, that the normal architecture of the gland may be lost. The cytology of the gland with special reference to the mitochondrial changes has been carefully studied by Key.¹

So far as is known at present, the stimuli that produce a demand for an increase in the function of the thyroid gland are numerous. Physiologically, such a demand occurs during puberty and adolescence, at menstrual time and during pregnancy. Certain dietary deficiencies have a marked effect, as has been shown by McCarrison.² Webster and Chesney³ have produced goiter in rabbits by feeding cabbage. Some

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* From the Department of Surgery, Washington University School of Medicine, and Barnes Hospital.

1. Key, J. A.: The Secretion Antecedents and Mitochondria in Pathologic Thyroids, *Arch. Surg.* **11**:254 (Aug.) 1925.

2. McCarrison, Robert: *The Simple Goitres*, New York, William Wood & Company, 1928.

3. Webster, B., and Chesney, A. M.: Studies in Etiology of Simple Goitre. *Am. J. Path.* **6**:275 (May) 1930.

time ago we⁴ showed that various types of infections and toxemias could produce these changes. More recently we demonstrated that hyperactivity of the gland could be caused by the injection of certain drugs, notably the methylated purines and related substances.⁵ Accordingly, we feel that various degrees of hypertrophy and hyperplasia of the thyroid gland with subsequent involution are extremely common. There are perhaps few organs in the animal body subject to more frequent and greater anatomic changes due to a transient increase in function than is the thyroid. These changes may take place in a comparatively short period of time. We have observed a marked transformation in as short an interval as eighteen hours. It may be in the form of an intense desquamation of epithelium and loss of colloid, so that the thyroid may be difficult to recognize as such microscopically, or if the stimulus is not so great the changes will not be so great and will be those of hyperplasia instead. If the stimulus is milder still, one sees acini with columnar cells, vascular congestion and thin, poorly staining colloid along with other evidences of increased activity of the thyroid gland. When a slight increase in activity is demanded over a long period of time, the changes frequently produced resemble, perhaps more than any other, those of exophthalmic hyperplasia. Apparently the amount of change produced in the gland depends on the strength of the stimulus and the time it is at work and the amount of colloid or iodine that is present in the thyroid or that is easily available. Intense changes in the thyroid gland occurring during an infection can be almost completely prevented by feeding the animal large doses of iodine. Likewise, we have found it more difficult to produce glandular changes in the summer when the thyroid is in a more complete resting phase and thus contains more iodine.

Since it is possible to produce hyperplastic changes in the thyroid gland experimentally, and since it is likewise possible to cause an artificial involution by the use of iodine or a natural involution by the withdrawal of the stimulus, it occurred to us that it would be of value to study the anatomic changes that occur in the gland by a repetition of this cycle.

4. Cole, W. H., and Womack, N. A.: Reaction of the Thyroid Gland to Infections in Other Parts of the Body, *J. A. M. A.* **92**:453 (Feb. 9) 1929. Cole, W. H.; Womack, N. A., and Gray, S. H.: The Thyroid Gland in Infections and Toxemias: Pathological Changes in the Human Gland, *Am. J. Surg.* **6**:221, 1929. Womack, N. A.; Cole, W. H., and Heideman, A. G.: The Thyroid Gland in Infections: The Effect Upon the Basal Metabolic Rate, *Endocrinology* **12**:733, 1928.

5. Cole, W. H.; Womack, N. A., and Ellett, W. H.: The Production of Hyperplasia of the Thyroid Gland by Chemical Means, *Arch. Surg.* **22**:926 (June) 1931.

METHODS AND MATERIALS

We used dogs in this experiment because of their accessibility, the size of the thyroid in this animal and the fact that excess scarring in the gland of a normal dog is unusual. Although tumors do occasionally occur in dogs, in the vicinity of St. Louis they are usually definitely neoplastic in type. As a control, the gland of each animal was inspected before the experiment was begun, and a small section was removed from the inferior pole of the right lobe for microscopic study. Those animals were discarded in which glands were not in the resting phase. The picture (fig. 7A) of a thyroid gland without nodules, visible scarring and in a resting phase we took as normal.

The amount of connective tissue in such a gland is noticeably less than that in the gland of an adult human being. The gland is surrounded by a rather thin capsule of areolar and fibrous connective tissue from which small trabeculae arise and extend centrally. The gland is rarely divided into lobules, as is often seen in man, for usually the connective tissue is difficult to demonstrate except in the proximity of the capsule and around larger blood vessels. It is generally stated, however, that a delicate reticulum of connective tissue extends along the smaller capillaries surrounding each follicle and forms a stroma for the gland. We were unable to demonstrate such a reticulum of connective tissue completely, even with the use of special stains. However, it is an extremely delicate network. By the use of the van Gieson and Mallory stains, Key¹ was able to demonstrate such a reticulum in human glands. The location of this fibrous tissue is important for, as we shall attempt to show, an increase in connective tissue is often associated with considerable anatomic distortion of the gland.

Hyperplasia of the thyroid was produced by the production of infections, the injection of drugs, chiefly methylated purines, and the implantation of contaminated foreign bodies over a long period of time. It is interesting to note that every acinus is not affected to the same degree during the production of hyperplasia. In one area one may see overwork to the point of cellular death while in an area closely adjoining there may be only a mild amount of increased activity on the part of the cells.

REPAIR

Apparently the thyroid gland has a remarkable power of regeneration similar to that of parenchymatous organs such as the liver and the kidney. Cells that are injured beyond repair are desquamated into the lumen of the acinus and are speedily replaced by newly formed thyroid cells. Figure 1 illustrates this method of repair. It is interesting to note that within five days after fairly extensive injury an excess amount of regeneration takes place and these new cells in turn are hyperactive. This is probably the most common type of repair, and, as it is associated with little injury to the connective tissue or vascular injury, fibrosis is not a notable feature.

When an entire acinus is destroyed, it is doubtful whether this is replaced. Compensatory hyperplasia probably takes place in the remaining acini. A counterpart to this is seen in the liver, when an entire lobule is destroyed, and in the kidney, when an entire tubule is injured: collapse of the supporting reticulum occurs. When



Fig. 1.—*A*, section taken from the thyroid gland of a dog with a severe infection of the leg. Note the loss of colloid and the desquamation of the cells into the lumen of the acinus. In most of the acini some of the epithelial cells still remain intact. *B*, section taken from the same dog five days later. The infection in the leg has largely subsided. Here one sees complete regeneration of the acinar cells with little or no scarring. The cells are columnar in type and show hyperplasia in several areas. Colloid is beginning to reappear.

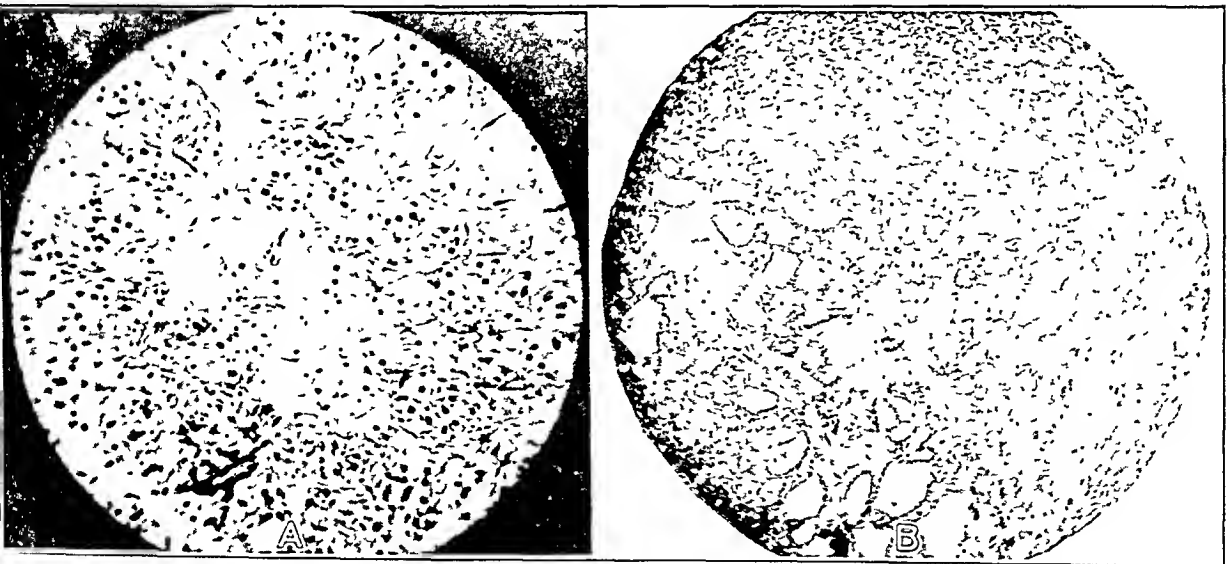


Fig. 2.—*A*, massive necrosis of the thyroid following administration of a large dose of caffeine alkaloid by mouth (0.15 Gm. per kilogram). Note the destruction of the entire acini. *B*, replacement of localized fibrous tissue in the thyroid of a dog following a severe infection.

injury is so severe, there is usually a varying degree of damage to the underlying stroma. This results in fibroblastic proliferation and, like such proliferation elsewhere, it is usually excessive. Figure 2*A* shows such an area of complete necrosis following a toxic dose of caffeine. Figure 2*B* shows the probable type of replacement of fibrous tissue that follows such a focal injury.

We found it difficult to produce the extensive diffuse perilobular fibrosis that is so commonly seen in the human gland following treatment



Fig. 3.—Encapsulated nodule involving the upper pole of the thyroid gland of a dog one month after laparotomy and a localized peritonitis. Previous examination of the gland had shown no nodules.

with iodine therapy in exophthalmic hyperplasia. This may be due to the scant amount of connective tissue occurring between the acini in the dog, as was mentioned in the early part of this paper. Consequently we did not produce the multinodular goiter that one often encounters. Certainly in our cases, most of the fibrosis seemed to emanate from those regions near larger blood vessels where connective tissue was normally more profuse. We were able to demonstrate fibrosis in scattered areas

and likewise we were able to demonstrate small so-called adenomas. The mechanism of the production of these nodules is probably the encircling of a group of acini by fibrous tissue with subsequent cycles of hyperplasia and involution. Figures 3, 4 and 5 show the formation of nodules encapsulated and similar in every respect to their counterpart in the human gland. The formation of these nodules was apparently in proportion to the amount of fibrosis in the gland. By producing a profuse ingrowth of fibrous tissue by means of the injection of a trypsin

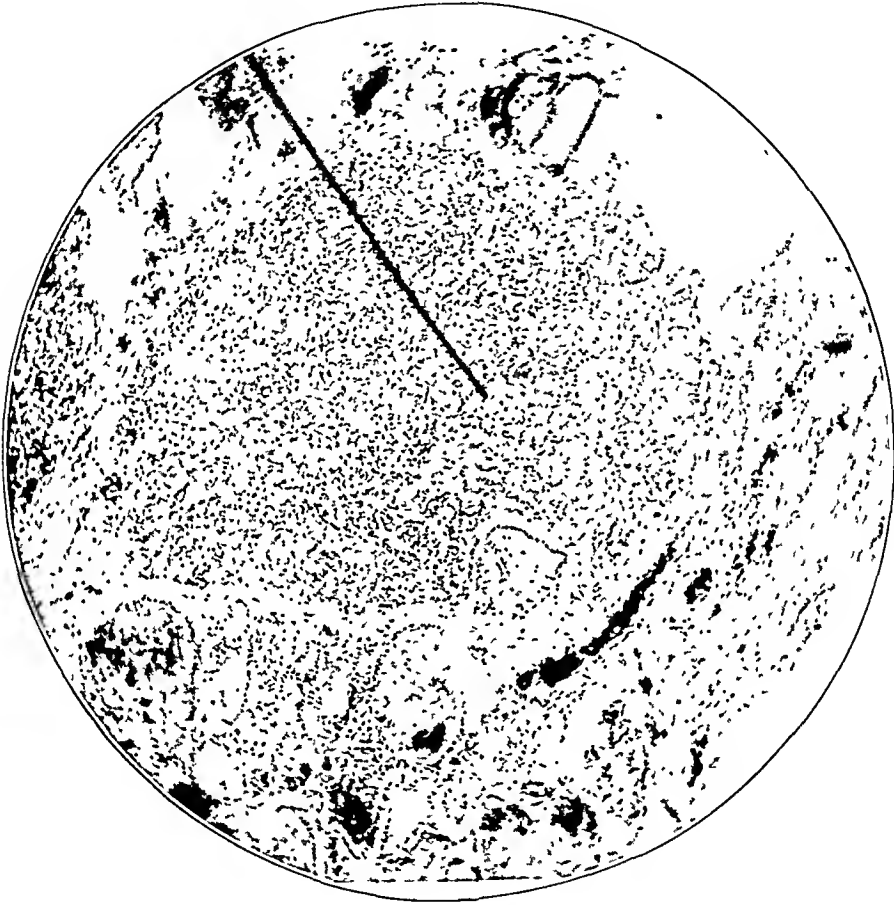


Fig. 4.—Section taken from the thyroid gland of a dog nineteen days after the injection of a solution of trypsin into the inferior thyroid arteries. There was a diffuse fibrosis throughout the gland. In this section one sees an "adenoma" formed by a group of acinar cells being cut off and surrounded by connective tissues. A previous section of the gland was normal. Inspection of the entire gland at that time showed no nodules.

solution into the inferior thyroid artery or by other methods, we noted nodular changes much more frequently. Some of these nodules resembled the so-called fetal adenoma in such detail that while we cannot disprove the theory of embryonic rest, we are inclined at the present

time to explain the presence of these nodules on the basis of morphologic changes as a result of a natural physiologic cycle. Although we have no proof that these adenomas were not already present in a microscopic form before our experiments were started, we wish to emphasize the fact that in sections taken from several hundred normal dogs in the past few years, we did not encounter a single instance of an adenoma.

We have shown in previous studies that iodine protects the animal to a large extent from these hyperplastic changes in the thyroid. Natu-

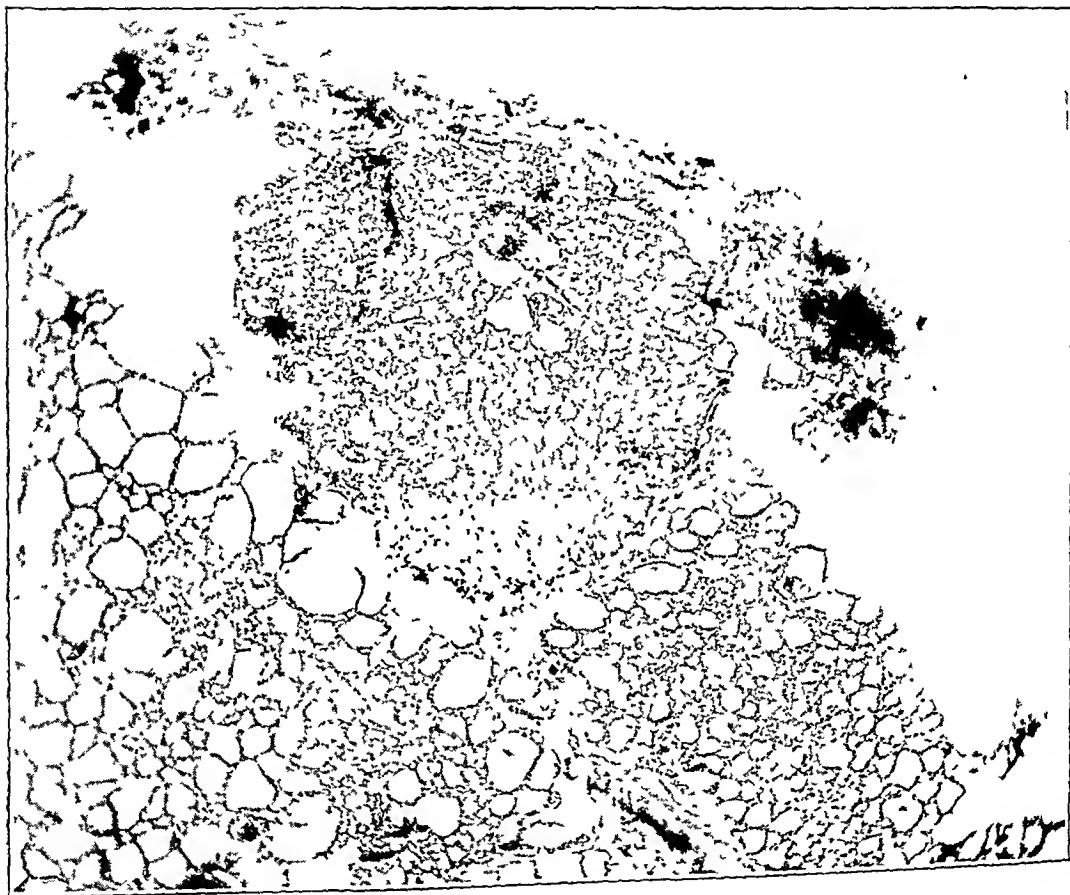


Fig. 5.—Nodule in the thyroid gland of a dog dying five days after the administration of a compound solution of iodine. This dog was emaciated, had a fever of 104 F., and was very ill when received. It no doubt was suffering from an infection of long duration. Gross examination at the time of the autopsy did not reveal the cause of death. There was no previous biopsy done on this animal.

rally, in such cases fibrosis does not occur (fig. 6). However, if the hyperplastic changes have been present for several weeks and the animal is then fed iodine, a certain amount of replacement of fibrous tissue takes place in spite of the fact that parenchymatous regression may be such that it is difficult to differentiate from the former sections of the

same gland in its resting phase. If the iodine is again withdrawn, hyperplasia will reappear and will persist until sufficient iodine is again given the animal or until the stimulus causing the change is withdrawn. Figure 7 shows such a train of events. Note the similarity of the final photographs to the structure of the thyroid in exophthalmic goiter.

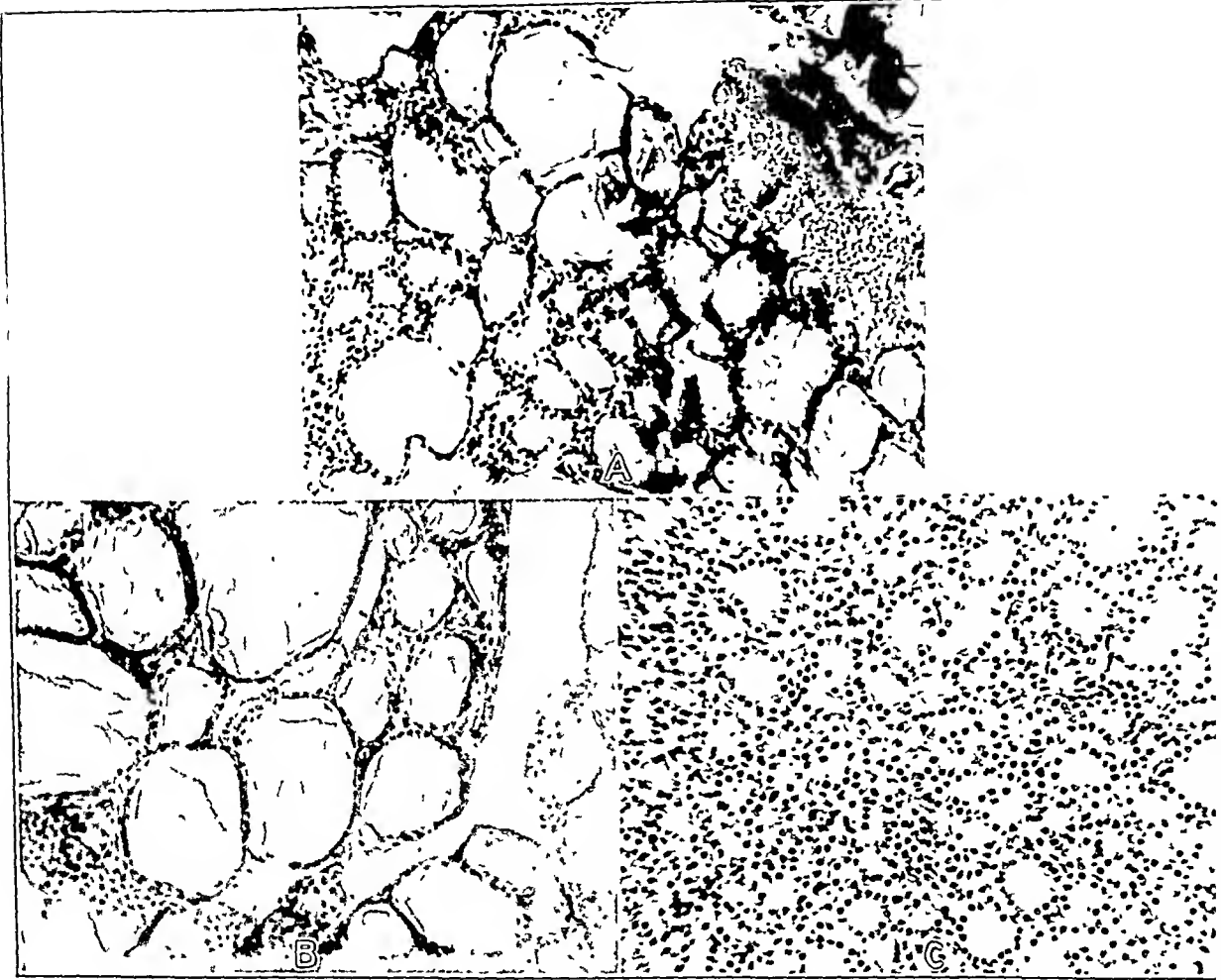


Fig. 6.—*A*, normal control section taken from the thyroid gland of a dog, after which a contaminated foreign body was buried in the muscles of the neck. The animal was then given a compound solution of iodine. *B*, section from the thyroid of the same dog after two weeks of administration of a compound solution of iodine. The gland shows no great amount of change, owing, we think, to protection offered by the iodine. Note the absence of scarring. No more iodine was given. *C*, section from the same animal thirteen months after the section seen in *B* was taken and with the chronic infection still in place. Note the hyperplasia and the loss of colloid. The cells are columnar, and the picture resembles that sometimes seen in exophthalmic hyperplasia in the human being. Note the absence of scarring.

These animals, as we have reported elsewhere, had a high basal metabolic rate, increase in pulse rate and some of the other clinical signs seen in toxic goiter.

COMMENT

If the foregoing facts apply to human beings, we should expect to find nodular goiters more common in those regions in which the supply

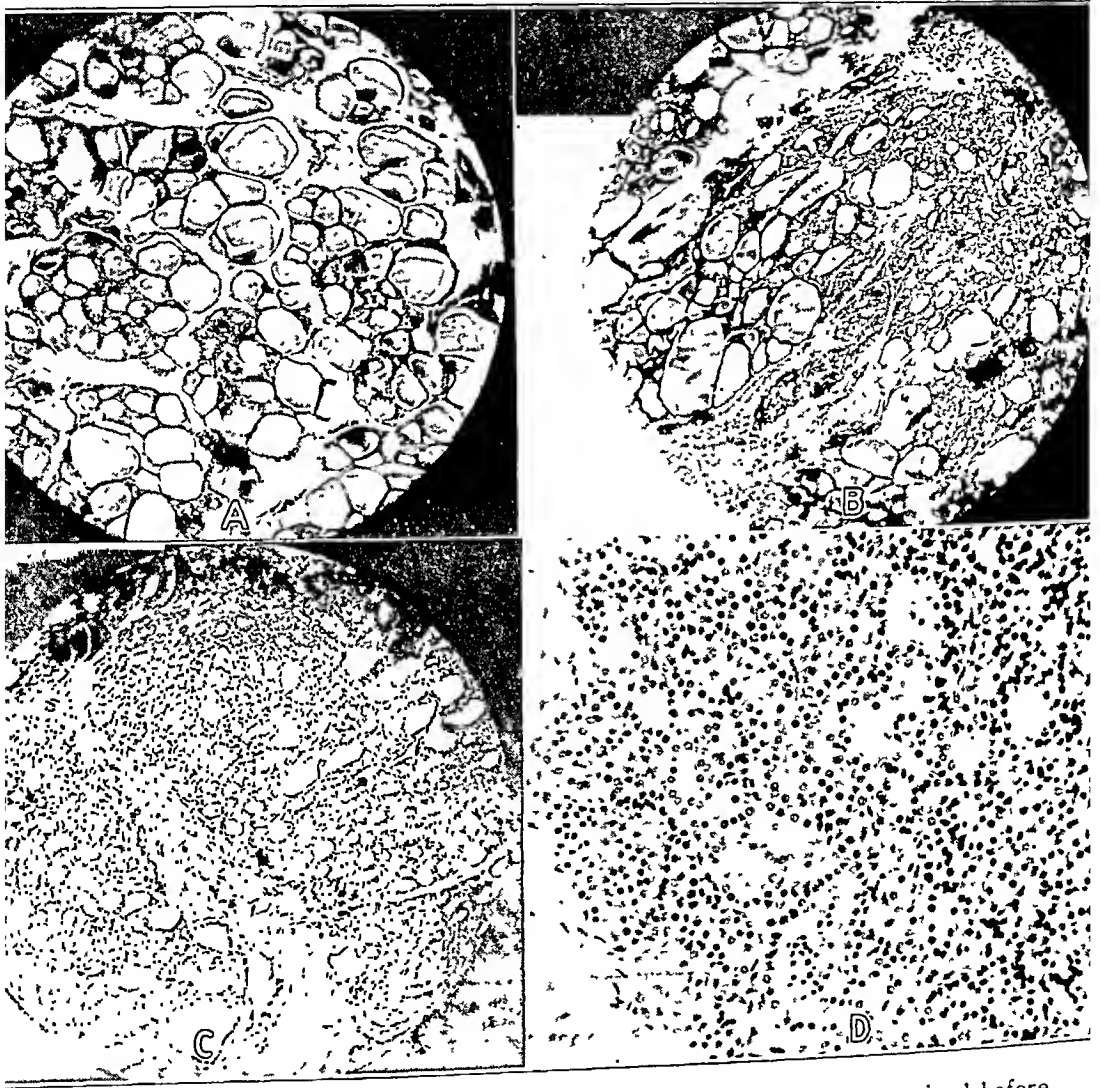


Fig. 7.—*A*, normal control section taken from the thyroid of an animal before the experiment was started. *B*, section from the same animal fourteen weeks later. Two weeks after a contaminated foreign body was buried in the muscles of the neck, compound solution of iodine was given for five days. This was continued and was fed to the animal again for two weeks before this section was made. Note the masses of fibrous tissue with acini showing both hypo-involution and hyperinvolvement. The administration of iodine was stopped. *C*, section from the same dog eight months later. Note the dense bands of scar tissue surrounded by active thyroid tissue. *D*, higher power magnification of section *C*, showing the hyperplastic columnar cells and a picture resembling that in figure 6*C*. This is the effect of a long-standing focus of infection in this animal.

of iodine is scant. We should expect this because marked hyperplasia with involution would be more common. This is, of course, the case. Likewise, we should expect to find nodular goiters more common as the age of the individual increases. This, likewise, is true. In a series of 41 consecutive autopsies on human beings, most of them adults and none showing clinical goiters, we found that only 26.8 per cent could be classified as having normal glands, if our old criteria for a normal gland were used. A large portion of this 26.8 per cent showed some scar tissue and even small areas of focal hyperplasia. While we can not go so far as to state that the age of the patient can be reckoned by a study of the thyroid, as has been claimed by some, we feel certain that these changes are more common in older people. Wegelin⁶ has demonstrated this conclusively in a long series of autopsies. He found, for instance, that at the age of 30 struma nodosa was present in 76 per cent of his 696 consecutive autopsies, struma diffusa in about 20 per cent and in about 10 per cent, the glands were found to be normal. This relationship was not constant, but varied with the age decades.

Until recently the opinion generally accepted in regard to the nature of the origin of the benign nodular goiters has been that they are true neoplasms, benign adenomas. This has been due not only to the striking morphologic similarity to adenomas elsewhere in the body but also to the difficulty in coordinating the clinical and pathologic pictures. Wölfler's⁷ theory of the persistence of embryonal rests even in the adult gland has been a most popular one in spite of the fact that little substantial proof for it was ever offered. More detailed anatomic studies⁸ have failed to demonstrate these interacinar fetal rests. It is, in fact, probable that the adult interacinar cells usually seen are tangential sections through other adult acini. Likewise, further clinical and pathologic studies⁹ by several investigators have shown conclusively that it is possible for these so-called adenomas to develop during the course of involution of an actively hyperplastic gland.

6. Wegelin, C.: Die Schilddrüse, in Henke-Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

7. Wölfler, A.: Ueber die Entwicklung und den Bau des Kropfes. Arch. f. klin. Chir. **29**:1, 1883.

8. Rienhoff, W. F., Jr.: Gross and Microscopic Structure of the Thyroid Gland in Man, Arch. Surg. **19**:986 (Dec.) 1929. Williamson, G. S., and Pearse, I. H.: Anatomy of Special Thyroid Lymph System Showing Its Relation to the Thymus, Brit. J. Surg. **17**:529 (Jan.) 1930.

9. Rienhoff, W. F., Jr., and Lewis, D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16**:79 (Jan.) 1928. Hertzler, A. E.: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. **16**:61 (Jan.) 1928. Dunhill, T. P.: Toxic Goitre, Brit. J. Surg. **17**:424 (Jan.) 1928.

SUMMARY

We should like to emphasize the following points:

1. Increase in the functional activity of the thyroid gland is extremely common and is dependent on a number of factors. This increase in function is usually associated with definite morphologic changes that may occur to an extreme degree. If the stimulus is great enough, these changes may take place during the course of a few hours. A more or less mild stimulation of the thyroid gland over a relatively long period of time may produce hyperplastic changes similar to those seen in exophthalmic goiter.

2. Following involution brought about by the disappearance of the stimulus causing the increase in function or by artificial involution due to the administration of iodine, replacement of fibrous tissue occurs.

3. Repetition of this physiologic cycle may produce a nodular goiter similar to the so-called adenoma. The occurrence and location of these nodules is apparently dependent on the amount and the location of the fibrosis.

4. Experimental evidence is offered in support of these facts.

PLASMA CELL TUMORS OF THE NASAL AND NASOPHARYNGEAL MUCOSA *

LOUIE N. CLAIBORN, M.D.

AND

HENRY W. FERRIS, M.D.

NEW HAVEN, CONN.

Most of the textbooks on pathology make little if any mention of plasma cell tumors except those occurring in the bone marrow, the plasma cell myelomas. Ewing,¹ however, in his work on neoplastic diseases, discussed extramedullary plasma cell tumors, and stated that in a rather numerous group of tumors of the mucous membranes and lymph nodes the growth is composed exclusively of plasma cells. He said:

Considering their comparative frequency and rather peculiar clinical course, they have received inadequate attention. The growths occur chiefly in the nasopharynx, alveolar borders, tongue, lips, and cervical lymph nodes, but they have been observed in many other regions. The course is relatively slow, but they may recur after extirpation and become associated with a chronic cachexia. They are commonly classed as lymphosarcoma, but being, as a rule, benign processes with very indistinct neoplastic properties, it is highly important that they should be separated from the malignant lymphosarcoma. The structure presents a diffuse growth of more or less typical plasma cells.

Kaufmann² mentioned some cases of plasmacytoma which he said are counterparts of plasma cell aleukemic lymphadenosis. These special cases show granulation tissue, composed almost exclusively of plasma cells and lymphocytes, not only in numerous lymph nodes, but also in the liver and bone marrow. According to him, "A local plasma-cellular lymphogranulomatosa, so-called plasma-cellular granuloma or plasmacytoma, with a tumor-like appearance, adopts its favorite site in the nasal mucosa."

CASES FROM THE LITERATURE

In reviewing the literature, we have been able to find only twelve instances in which plasmacytomas of the nasal mucosa or nasopharynx have been described.

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* From the Departments of Surgery and Pathology, Yale University, School of Medicine.

1. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 420.

2. Kaufmann, E.: *Pathology*, transl. by Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 272.

In 1905, Schridde,³ in a paper discussing granules in plasma cells, stated that he secured some of the material for the study from a tumorous involvement of the nose in a 40 year old man. The mass was found to consist of nests of plasma cells, between which capillaries were present. He gave no further details as to the clinical or pathologic observations.

Von Werdt,⁴ in 1911, described the case of a 69 year old man, who had nasal speech and difficulty in swallowing, and who finally consulted a physician because of the former. A walnut-sized, freely movable tumor was found projecting from the posterior surface of the uvula. The outer surface was nodular and bluish red. There was no swelling of the glands of the neck. The mass was removed with a cautery snare. The wound healed quickly, and no recurrence of the process was evident at the time the case was reported. Pathologically, the tumor showed a transparent grayish-yellow outer portion and a central reddish-gray zone, the latter showing streaklike hemorrhages. The tumor was quite firm. Microscopically, it was seen to consist practically entirely of plasma cells, some of which showed mitoses, and other several nuclei. Cells with pyknotic nuclei and red bodies in the cytoplasm were found. (Hoffmann called these degeneration cells.) The capillaries were numerous; the stroma was scanty and contained pigment granules and hemorrhages.

In 1912, Vogt⁵ wrote of a 20 year old man who had a rather sudden onset of pain in the neck and hoarseness. Examination revealed a tumor mass extending from the mastoid process to the jugular fossa, along the sternomastoid muscle. The structure was hard and freely movable. The posterior cervical nodes were not increased in size. The patient died in a "choking fit" four days after admission to the hospital. Autopsy showed that the posterior pharyngeal wall and the soft palate were almost double in thickness and seemed stiff and unyielding. The tonsils were swollen to walnut-sized masses which narrowed the pharyngeal passageway. On section, one could see that the thickening of the tissue was due to a pale gray infiltration of the submucosa by small nodules. Because of the great infiltration of the epiglottis, a stenosis of the laryngeal passage had been brought about. The thickening extended to the false vocal cords. The cervical lymph nodes on each side were the size of a walnut, not fused and easily removed. The cut surface was grayish and moist. In one node, pinhead-sized yellow masses were noticed. The axillary nodes were somewhat swollen, but those at the hilus were not enlarged. Microscopically, the uvula showed beneath the epithelium of its mucosa an infiltration of cells mostly of lymphocytic and plasma cell types. The latter frequently formed marked perivascular zones. The plasma cells were mostly of the usual type with an eccentric nucleus the chromatin of which presented a cartwheel-like arrangement. In many of the cells a perinuclear clear zone of cytoplasm was present. Sometimes cells with two nuclei located diametrically opposite in the cytoplasm were seen. More than two nuclei were only occasionally observed. Some cells had dark-staining nuclei. In a few areas the plasma cells were elongated and spindle-shaped, resembling fibroblasts. In the deeper portions of the mucosa, multinucleated giant cells of the Langhan's type were found in tissue infiltrated with lymphocytes and containing numerous vesicu-

3. Schridde, H.: Weitere Untersuchungen über die Körnelungen der Plasmazellen, *Centralbl. f. allg. Path. u. path. Anat.* **16**:433, 1905.

4. von Werdt, F.: Zur Kenntnis des Plasmocytoms, *Frankfurt. Ztschr. f. Path.* **6**:180, 1911.

5. Vogt, E.: Granulomatosis plasmacellularis colli, *Frankfurt. Ztschr. f. Path.* **10**:129, 1912.

lar nucleated epithelioid cells. No acid-fast bacilli were found. The posterior pharyngeal wall showed a picture similar to that in the uvula, except that no giant cells or epithelioid cells were present. The plasma cells extended along the blood vessels into the musculature, where they formed thick conglomerations of cells in the septums. The posterior part of the tongue, the epiglottis and the laryngeal wall showed marked infiltrations of plasma cells and also lymphocytes and a few polymorphonuclear leukocytes. The cervical lymph nodes were rich in plasma cells, especially near the fibrous capsule. A few of the nodes contained giant cells. The axillary nodes, inguinal nodes and the spleen likewise showed an increase of plasmacytes, but no Langhan's cells. Guinea-pigs given injections with the material showed no tuberculosis when killed later.

A fourth case was reported by Kusunoki and Frank⁶ in 1913. This case was subsequently reported the same year in a different journal by Frank.⁷ A man, aged 44, had noticed two years previously, at the angle of the left jaw, a pea-sized, hard mass. This became larger, and new masses appeared. The patient did not consult a physician until a year later, at which time respiratory difficulty was experienced. Roentgen therapy was given without results. About a year before admission the patient noticed tumors in his nasopharynx, and it became impossible for him to breathe through his nose. Epistaxis was a troublesome symptom. During two years he lost from 80 to 90 pounds (36.3 to 40.8 Kg.). The tumor of the left side of the neck was removed, and a month later that in the nasopharynx. The tissue from the latter consisted of ten pieces, the largest of which measured 3.5 by 3 by 1 cm. The remainder were about the size of an almond. The surfaces were irregularly nodular, firm but elastic, and varied from grayish white to grayish brown. The nodular masses were easily separated from the surrounding tissue. The cut surface was smooth, not protruding, and of the same color as the outer surface. On microscopic examination, a large number of typical plasma cells were found, especially grouped about blood vessels and capillaries (the latter being so rich as to give the structure a honey-combed appearance). Areas of necrosis were observed. The mucosa was preserved in scattered places while the submucosa showed a granulation tissue with some hemorrhage and some acellular hyaline connective tissue. The tissue from the neck consisted of twenty pieces which had not fused together, but were surrounded by loose connective tissue. The largest of these was 8 by 4.5 by 3.5 cm., the smallest about the size of a pea. The nodes were firm, nodular and grayish white. The cut surface was uneven and divided into many divisions by small and large white bands of connective tissue. In these places the larger masses were a dirty gray and showed rather poorly demarcated areas of necrosis. Microscopically, lymphoid structure was found preserved in only a few places. Plasma cells had almost completely replaced the lymphocytes. The remaining lymphoid tissue appeared atrophic with only a few follicles showing mitoses in the germinal centers. In some instances the differentiation between plasma cells and lymphocytes was not sharp. No transitional cells between these two types were found, however. Some plasma cells contained two, but rarely more, nuclei. In a few of

6. Kusunoki, M., and Frank, A.: Ueber ein plasmazelluräres Granulom, unter dem klinischen Bilde von Lymphomen der Halslymphdrüsen und geschwulstartigen Knoten in der Nasenschleimhaut, *Virchows Arch. f. path. Anat.* **212**: 391, 1913.

7. Frank, A.: Ueber ein Granuloma plasmacellulare. (Unter dem Bilde von Lymphomen in dem Halslymphdrüsen und geschwulstartigen Knoten in der Nasenschleimhaut), *Verhandl. d. deutsch. path. Gesellsch.* **16**:115, 1913.

the plasmacytes were seen small, round, hyaline masses, the so-called "Russell bodies." Occasionally, these were present extracellularly. Mitotic figures were never encountered in the true plasma cells. The latter were grouped especially about blood vessels and were at times seen in the walls and even in the lumina. Capillaries were plentiful. Hemorrhages and areas of necrosis were observed. The patient died four years after the beginning of his illness, and showed at that time a swelling of the upper part of the thigh which was thought possibly to be also a plasmacytoma.

In 1913, Wachter⁸ cited the case of a 48 year old woman who had suffered from bilateral deafness following attacks of cerebrospinal meningitis and otitis media. Twenty years before her admission, the present condition began with slight hoarseness noticed after prolonged talking, and with pain in the neck. On the present admission to the clinic, examination revealed a hard, slightly nodular tumor which arose from the floor of the right nasal cavity and from the inferior turbinate. It was clearly separated from the nasal septum. The middle turbinate showed a grayish-red unevenness. The tumor was reddish and bled slightly on motion. In the left nasal fossa, arising from its floor, was a small, hard swelling covered by normal mucosa. By means of posterior rhinoscopy, there was found on the posterior surface of the velum directly over the uvula a cherry-sized tumor, covered with normal mucosa, and situated on a narrow base. On the left false vocal cord, a red granulating growth with a broad base was found. The growths were excised but recurred locally about five and a half months later, with the addition of a new mass near the opening of the left eustachian tube. About ten months later, a mass the size of a cherry was found near the eustachian tube, and the growth in the right nasal fossa was seen to be increased in size. On the left, a thick fold of mucosal tissue was present. The velum and uvula were free. On microscopic examination, the tissues excised were seen to consist of large masses of plasma cells. These cells showed the usual eccentric nuclei with radially arranged masses of chromatin, and were quite uniform in size. Cells with two nuclei and a few with several, the so-called "plasma giant cells," were observed. Vacuolated cytoplasm was found in some. The plasmacytes were especially abundant about the walls of blood vessels where interstitial tissue was often lacking. The masses of plasma cells were divided into rectangular lobules by bands of connective tissue. In a portion consisting of a loose edematous reticular tissue, round cells, mast cells, dark-staining granules, as well as a few plasma cells, were seen.

The only instance of nasopharyngeal plasmacytoma we have found reported in English was that of Rogers⁹ in 1920. He wrote of a 42 year old man, who about one year before had first noticed slight bleeding from the left nostril and the back of the nose. This continued for six months, when more severe hemorrhages from the nose and nasopharynx began. These hemorrhages commenced spontaneously, lasting from one to two days. About this time complete nasal obstruction occurred. At no time was there any pain. During the first year he sought advice from several physicians who prescribed nasal ointments or cauterized the nose. When seen by Rogers, he was anemic and the nasal obstruction was pronounced, but the septum was straight. The turbinates were pale and swollen, and a careful intranasal examination failed to reveal any bleeding points or

8. Wachter, H.: Ein Fall von multiplem Plasmazytom der oberen Luftwege, Arch. f. Laryng. u. Rhin. 28:69, 1913-1914.

9. Rogers, J. T.: Plasmoma of Nasopharynx, Canad. M. A. J. 10:223 (March) 1920.

pathologic growth. Posterior rhinoscopy, however, demonstrated an uneven, granular-appearing, hemorrhagic mass completely filling the nasopharynx and seeming to arise from its vault. The surface of the tumor showed areas of fresh and old hemorrhage. On admission, the hemoglobin was found to be 40 per cent. General physical examination gave negative results. Both external carotids were ligated, stopping the hemorrhage. Six weeks later the growth was removed intact by means of a snare. Subsequent examination showed that the tumor took origin from the inferior border of the cushion of the eustachian tube and the adjacent surface of the soft palate. Microscopic preparations revealed that the growth consisted essentially of plasma-like cells, which were large and contained small, round, eccentric nuclei. There was little ground substance, and the surface was covered with transitional epithelium.

Facchini and Scalas,¹⁰ in 1925, reported a plasma cell growth in a 47 year old woman. She had been married fifteen years and had never been pregnant. Her husband had acquired syphilis before marriage, but had had four years of intensive antisyphilitic treatment. At marriage his Wassermann test was negative, as it was at the time the case was reported. The patient for two years complained of difficulty in breathing through the right side of the nose. There had been no purulent secretion or other disturbance. On objective examination, it was noted that the right nasal cavity was completely occluded by a polypoid mass with a smooth, gray surface. The Wassermann and Meinicke tests were negative. The blood counts were normal. The tumor, which was attached to the upper and posterior part of the septum, was removed with little hemorrhage. The wound healed rapidly, and examination one year from the time of operation showed the nasal cavity to be free from any alteration except a slight cicatricial depression. The patient was given injections of mercuric chloride, following which the Wassermann reaction of the blood was again found to be negative. On gross examination, the tumor was found to measure 4 by 2 cm. The external surface was regular and smooth, and covered by a light red mucosa. The consistency was fibro-elastic. Around the base of the tumor were inserted small, round nodules of softer consistency and darker red color. On section, distinct zones could be observed with the naked eye or with only slight magnification. The peripheral part of the mass had a homogeneous aspect, gray and shining, that resembled the appearance of a common fibromyxomatous polyp. In the central regions were well circumscribed white islands of tissue, opaque and friable. The nodules in the vicinity of the pedicle also had these characteristics. The cut surface was gray and finely granular. Microscopically, a fine trabecular structure delineated areas of varying size containing the cellular elements. These were arranged some times in an alveolar manner and at other times in a cordlike fashion. The blood vessels were rather scanty with thin walls. The cells were oval or round, except where closely packed, when they were polygonal. The appearance of the nuclei and cytoplasm was typical of plasma cells except that perinuclear clear zones were not frequently observed. With the Unna-Pappenheim methyl-green pyronin stain, however, the characteristic reaction of the cells was seen. Giant cells containing two, three or more nuclei were occasionally encountered. A few large cells with less darkly staining nuclei and large nucleoli, others with pyknotic nuclei, and still others with vacuolated cytoplasm, were found. Mitotic typical and atypical figures were numerous.

10. Facchini, G., and Scalas, A.: Su di un caso di fibro-mixo-plasmocitoma della cavita nasale, *Arch. ital. di otol.* 36:331, 1925.

The observations made at autopsy on a 54 year old man who died several days following the partial extirpation of a tumor that filled the nasopharynx were described in 1926 by Rössle.¹¹ One tonsil and the nasal mucous membrane showed a widespread streptococcus lymphangitis. The tumor had grown through the clivus, filled the sphenoidal sinus, and reached past the roof of the pharynx to involve the upper part of the left nose. Two masses of tumor tissue were found on the posterior surface of the soft palate and two on the mucosa of the right antrum of Highmore. All the cervical lymph nodes and the sternum, ribs and skull showed neoplastic masses. Microscopically, all the growths were seen to be composed essentially of masses of plasma cells of different sizes, with a fine reticulum between the masses.

Hückel,¹² in 1927, discussed the case of a 46 year old workman who had had difficulty in breathing through his nose for six months, leading to an almost complete obstruction of the air passages. In his youth he had suffered from cervical adenitis. The general physical examination was without significant results. Rhinoscopic inspection showed a growth completely filling the whole nasopharynx with a small process the width of a finger extending down below the soft palate from a firm red mass. The right nasal cavity was narrowed by a deviation of the septum, while the posterior part of the left nasal cavity was obstructed by the growth. The mucosa of the pharynx and of the turbinates on both sides showed a slight catarrhal swelling. The maxillary sinuses were not involved. The growth was removed in several stages, partly through the nose and partly through the mouth. Bleeding was slight, and nasal respiration was restored. The origin of the growth was the mucosa of the posterior edge and of the wings of the vomer, and also of the nasopharynx. The thirteen pieces of tissue removed varied from the size of a pea to that of a bean. The external surfaces were partly dark brown and partly grayish white. They were unevenly nodular and fairly firm. The cut surfaces showed a similar appearance, were not very moist and were grayish white with here and there grayish-brown areas. On microscopic section, a rather uniform picture was seen, consisting of plasma cells packed closely together with a fine reticulum of connective tissue. In other places the stroma was denser and less cellular. In some areas the plasma cells formed columns between the dense strands. The plasmacytes contained often two, but seldom three nuclei. In rare instances mitotic figures were seen, but never amitotic division. A marked difference in the sizes of the plasma cells was not evident. Degenerative processes in the cells and "Russell bodies" were not found. The tissues were not especially vascular, and no particularly close relationship between the plasma cells and the vessels could be seen.

In the same year Pallestrini¹³ described the interesting case of a man, 43 years of age, who for five months had had obstruction of the right nasal cavity and a purulent discharge. He also had had intermittent frontal headaches and pain occurring in the region of the distribution of the first and second division of the right trigeminal nerve. The remainder of his history was essentially unimportant.

11. Rössle: *Malignes Plasmoytom des Nasenrachenraumes*, *Schweiz. med. Wchnschr.* **56**:302, 1926.

12. Hückel, R.: *Ueber ein Plasmacytom des Nasenrachenraumes*, *Virchows Arch. f. path. Anat.* **264**:172, 1927.

13. Pallestrini, E.: *Su di un plasmoma atipico e maligno del naso*, *Arch. per le sc. med.* **51**:175, 1927.

On physical examination, the positive signs were limited chiefly to the region of the head and neck. The right eye showed a mild exophthalmus. Vision and ocular movements were normal. There was a slight swelling in the right lower molar region. On examination of the nose, an enlargement of the inferior half of the right lateral wall was seen. The right cavity was completely occluded to the end of the vestibule by a pallid rose-colored neoplasm. The tumor was soft and showed some superficial ulcerated areas which were partially covered by pus. Some lymphadenopathy of the lateral cervical, supraclavicular, axillary and inguinal nodes was noted. The epitrochlear nodes were not enlarged. There were no clinical signs suggestive of syphilis. The Wassermann test was negative. At operation, the tumor was found to extend from the internal border of the right maxillary sinus to the region proximal to the inferior meatus, the inferior turbinate and the middle meatus. The maxillary sinus contained none of the neoplasm; however, pus was obtained from it as well as from the ethmoid cells. Grossly, the tumor consisted of a semi-oval, soft rose-gray mass the size of a walnut. Externally, it presented an irregular surface with many small round or oval ulcerations, which had irregular raised borders and were covered by a bloody and purulent exudate. The deeper portions were coppery red, and here and there many small soft areas were present. Microscopic preparations showed superficially a delicate connective tissue throughout which tumorous cells were seen. Those predominating were of the plasma-cellular type. Some of these were about the size of small lymphocytes; others were larger and round or oval. Some were irregular and had extensions of the protoplasm in fibrils which occasionally joined with similar processes from other cells. The nuclei of the first group were multilobulated. In some areas the cells were seen in chain formations separated in places by a delicate stroma directly surrounding the cells. Other areas showed epithelioid cells rich in protoplasm with single round nuclei, rich in chromatin. Throughout, some areas contained relatively few, small blood vessels, while in others a richness of blood vessels was noted. The patient returned to his home shortly after the operation. He was examined fifteen days later, and at this time a partial stenosis of the nasal cavity was found. He refused to submit to either a radical operative procedure or roentgen therapy. He died of cachexia and terminal meningitis six months later. Metastasis to the eyes had occurred.

Bronzini,¹⁴ in 1928, described a case of a man 53 years of age who for four years had been suffering from nasal obstruction, mucopurulent nasal discharge and frequent sneezing. The positive physical signs were limited to the chest and nasopharynx. Examination of the chest revealed decreased phonation at the apex of the right lung and in the right interscapular region with also a slight increase of tactile fremitus in these areas. Roentgenograms demonstrated an opacity at the apex of the right lung and an engorgement of lymph nodes of the hilus of the right lung. On rhinoscopic examination, an irregular tumor mass was seen which arose from the region of the inferior turbinate and completely occluded the right nasal fossa. The tumor was soft and bled easily. Bleeding was not materially lessened by the application of epinephrine. The left inferior turbinate was moderately hypertrophied. The laboratory findings were within normal limits, and the Wassermann test was negative. At operation, the mass, together with the right inferior turbinate, was removed. The postoperative course was uneventful. On subsequent

14. Bronzini, A.: Di un voluminoso granuloma plasmacellulare del naso, *Arch. ital. di otol.* **39**:449, 1928.

examination eight months later, no recurrence of the growth was observed; the site of the scar, however, still appeared fresh as though the operation had been done only a few days previously. It presented a granular surface, which was hemorrhagic and necrotic in places. A foul-smelling, grayish discharge from the rhinopharynx was noted. The patient was asked to return for further treatment, but refused; he died a short time later of bronchopneumonia. Histologic examination of the tissue removed at operation showed it to consist externally of nasal mucosa. Beneath this there were trabeculae of connective tissue between which large masses of typical plasma cells were found. These masses were seen especially around blood vessels. Occasional cells with two nuclei were noted. No epithelioid or giant cells were present. Peripherally, some lymphocytic infiltration was observed. The microscopic preparations revealed no areas of degeneration or atypical proliferation.

Borri,¹⁵ in 1928, presented two cases of plasma cell tumor. One was found in a 32 year old woman who had a history of syphilis, and occurred in the oropharynx. Because of its location and the fact that the diagnosis was not substantiated by microscopic studies, we are not including it in this series.

The second case was that of a man 56 years old who entered the hospital in December, 1923. At that time the right tonsil was found to be markedly hypertrophied, cryptic and pale. On the posterior pharyngeal wall was seen a neoplastic mass the size of a small almond, the structural characteristics of which were the same as those of the tonsil. Except for cervical lymphadenopathy, the remainder of the physical examination gave negative results. At operation the mass was removed and a tonsillectomy done. In 1926, the patient became aware of a sense of occlusion of the left nasal fossa. This early became complete. The patient was treated by a specialist who removed a large "meaty" mass. Following this the patient was well for two years, when the condition recurred. A similar operation was performed, which afforded relief for about a month and a half, at the end of which time the patient again began to have nasal occlusion and difficulty in deglutition. In November, 1928, he again entered the hospital for treatment with radium of a supposedly malignant tumor of the right tonsil. Examination of the oropharynx showed the right palatine tonsil to be markedly hypertrophied, cryptic, pale and divided into numerous lobes by fibrous septums. In places the mucosa showed definite ulceration. The tonsil had a hard, rubbery consistency to palpation. Rhinoscopy revealed in the left nostril a large, "meaty" pale mass with an irregular surface, which also showed some ulceration. Aside from the complaints described, the patient had always been in good health until the last year, when he became mentally senile. The Wassermann test was found to be positive. In the latter part of November the right tonsil was completely enucleated, and a biopsy was taken from the nasal tumor. Microscopically, the tonsil and nasal tumor mass showed much the same picture. The deeper tissue showed a marked infiltration with an irregular round cellular element. In many of the cells the cytoplasm was granular, showing perinuclear semilunar lighter-staining areas. The nuclei were peripherally arranged, and the chromatin consisted of small triangular blocks, with their apexes pointing toward the center of the nucleus. In the center a small block was present, from which the other masses of chromatin radiated. In some areas, particularly surrounding blood vessels, numerous lymphocytic elements were

15. Borri, C.: *Plasmomi delle fosse nasale e della faringe*. Valsalva 5:416, 1928.

present, some of which suggested plasma cells. The blood vessels, which were relatively infrequently seen, showed a proliferation of the intima and a poorly developed adventitia. While waiting for the tonsillar fossa to heal, the patient received insufflations of bismuth and arsphenamine powders. After ten days of treatment the nasal tumor was found to be reduced to one-third its original size. Later bismuth and iodine was given. On Dec. 30, 1928, on reexamination, the operative site was found to be healed, and the nasal growth to have disappeared.

AUTHORS' CASES

We wish to report two cases of plasma cell tumor of the nasal and nasopharyngeal mucosa which we have had the opportunity of studying.

CASE 1.—A Polish man, aged 34, came to Dr. Hammond's office with a complaint of "nose trouble" which had been present for years. Otherwise his history was essentially unimportant. Aside from the nasal condition, the general physical examination revealed nothing of note. A rhinoscopic study, however, demonstrated an irregular, gray tumor mass which filled the entire interturbinate space in the right nasal fossa. This appeared to arise from the turbinate bones. The tumor was partially covered by a yellowish-gray exudate. The entire tumor was removed at operation, and the wound healed nicely. Subsequent examinations, the last a year and a half after operation, did not reveal any evidence of recurrence.

Pathologic Study.—Gross: The specimen consisted of four irregular pieces of tissue which averaged about 2 cm. in diameter. They had been preserved in alcohol and were opaque and yellowish gray. On section, the cut surfaces presented an uniform, soft gray appearance.

Microscopic: The material was fixed in alcohol and a solution containing 1 part of "solution of formaldehyde U. S. P." and 9 parts of water. A portion was embedded in celloidin and another in paraffin. The preparations were stained with hematoxylin-eosin. No Unna-Pappenheim methyl-green pylonin or other special stains were made. In some of the microscopic preparations the external surface of the tissue was seen to be partially covered by a thin layer of stratified squamous epithelium. Beneath this, numerous moderately thick trabeculae of fibrous tissue, containing oval or spindle shape cells, divided the tissue into rather small irregular areas which were loosely filled with cells. The latter consisted chiefly of rather small round or oval cells with homogeneous grayish-blue cytoplasm containing spherical nuclei, many of which were eccentrically located. The chromatin of these nuclei had a radial arrangement which gave the so-called cartwheel appearance. These appeared to be typical plasma cells and were for the most part fairly uniform in size and shape. Here and there, however, larger cells which were about twice the size of the surrounding cells, but which were otherwise identical in structure, were seen. An occasional larger cell containing two nuclei was found and rarely those containing three nuclei were present. Scattered throughout the large groups of cells fairly numerous lymphocytes and polymorphonuclear cells were seen. There were also found irregularly throughout, fairly numerous, rather large, round or oval cells which had sharp margins and poorly staining vacuolated cytoplasm. These contained small, oval, somewhat vesicular nuclei. This type of cell was extremely difficult to classify. In no place did the plasma cells appear to invade the septums of fibrous tissue. Anaplasia was not distinct; no mitotic figures in the plasma cells were seen and no areas of hemorrhage or frank necrosis were found. In several areas capillaries were rather numerous.

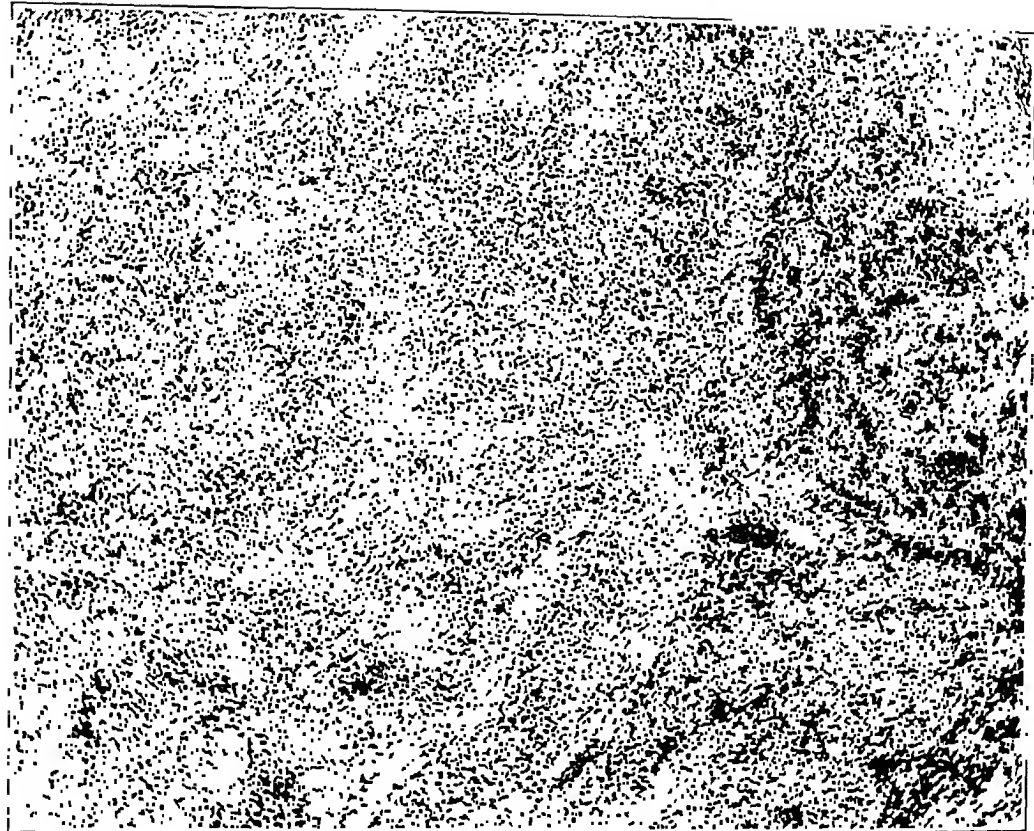


Fig. 1 (case 1).—Photomicrograph showing dense distribution of plasma cells. The stroma is fairly dense. Hematoxylin-eosin stain; $\times 75$.

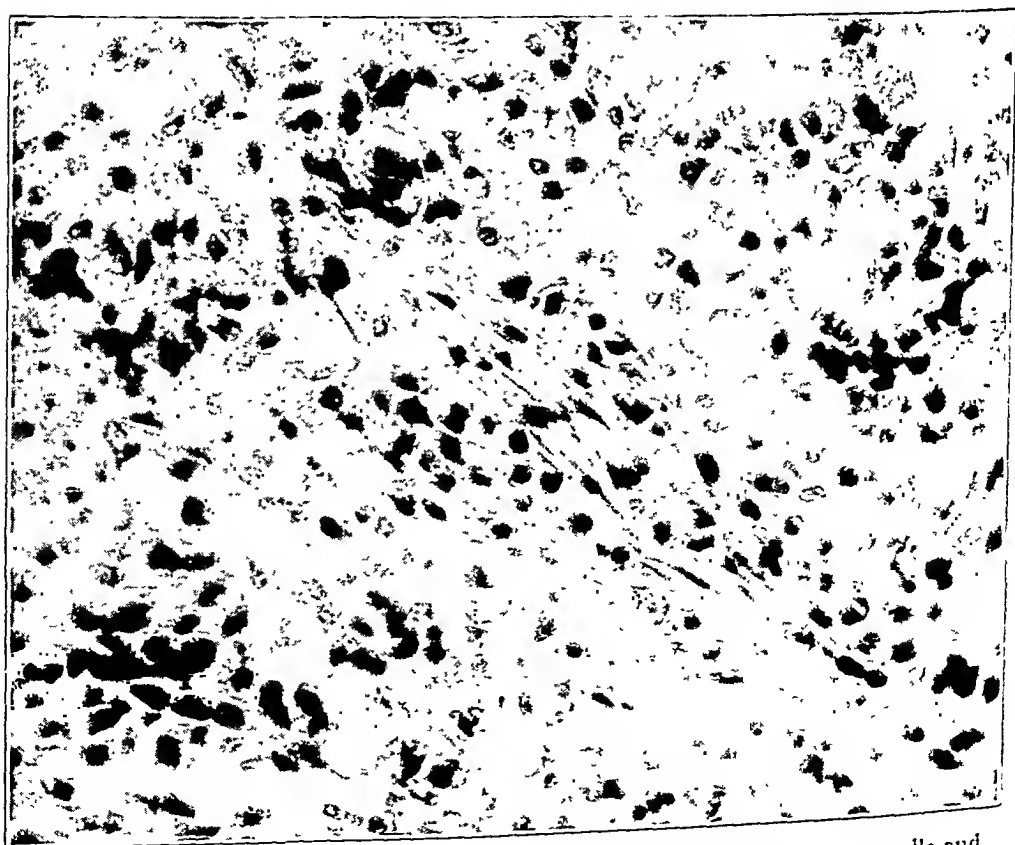


Fig. 2 (case 1).—Photomicrograph showing in more detail the plasma cells and the rather marked fibrous stroma. Hematoxylin-eosin; $\times 300$.

CASE 2.—A man, aged 60, a native of Sweden, on admission to the New Haven Hospital, May 5, 1930, gave the following history: For the past two years the right side of his nose had been obstructed, and he had noticed a moderate post-nasal discharge. He had used nasal drops for some time with no improvement of symptoms. In September, 1929, a small "growth" was removed from the right nasal fossa. The clinical diagnosis at that time was nasal fibroma. No pathologic examination of the tissue was made. Following the operation the patient had some relief from symptoms, which, however, lasted only a short time. The symptoms again became marked, and on examination it was found that the tumor had recurred. The patient had no headaches or dizziness. He gave a history of having had severe attacks of tonsillitis occurring almost every winter for several years. About two weeks before admission, a small tumor was removed from under his left arm. No pathologic examination of the tissue was made. The remainder of his history was irrelevant.

On physical examination the patient was seen to be moderately well developed and well nourished. Except for the nasal condition, the physical examination gave essentially negative results. On inspection of the nose, the septum was seen to be somewhat deviated to the left and in contact with the left middle turbinate. Both inferior turbinates were enlarged. The right middle turbinate was moderately hypertrophied. In the right nasal cavity a raised, somewhat lobulated tumor mass, about 3 cm. in length and 1.5 cm. in width, was seen extending from the middle meatus over the middle turbinate. It was partially covered by a yellowish exudate. A similar but somewhat smaller tumor mass was seen extending downward from the fossa of Rosenmüller on the right. The Wassermann test and urinalysis gave negative results. The blood count showed: red blood cells, 5,400,000; hemoglobin, 110 per cent (Sahli); white blood cells, 8,000, with a differential count of 59 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes and 7 per cent large mononuclear cells. Roentgenograms of the nasal sinuses were negative, and no pathologic process of the bone was demonstrated in the skull. The clinical impression was fibroma of nasopharynx. On May 6, 1930, under local anesthesia, incisions were made on either side of the tumors with alligator scissors, and they were then removed by means of a snare. Only moderate bleeding was encountered. Three days later the sites of the tumors were irradiated, 33.75 millicurie hours of irradiation being used. Following this, the patient was discharged. Subsequent examinations showed the operative sites to be healed. To date there is no evidence of recurrence (12-1-30).

Pathologic Study.—Gross: The gross specimen consisted of several pieces of tissue, the largest of which measured about 4 by 2 by 1 cm. Externally, the tissue was grayish white and smooth. To palpation, the tumor felt moderately soft. On section, the tissue cut easily, the cut surfaces presenting a gray fibrous appearance, throughout which numerous rather large dark bluish-red hemorrhagic areas were seen.

Microscopic: The material was fixed in neutral formaldehyde, 10 per cent, and preparations stained with hematoxylin-eosin and methyl-green pyronin. Others were stained according to Mallory's and to van Gieson's technic for connective tissue, and by Haythorne's and Kinyoun's methods for spirochetes and acid-fast bacilli, respectively. Several of the microscopic preparations showed the nasal mucosa, consisting of an epithelial portion with a surface layer of columnar epithelium, occasionally showing cilia, and one or two rows of more basally located cuboidal cells. Below this there was a layer of rather loosely arranged

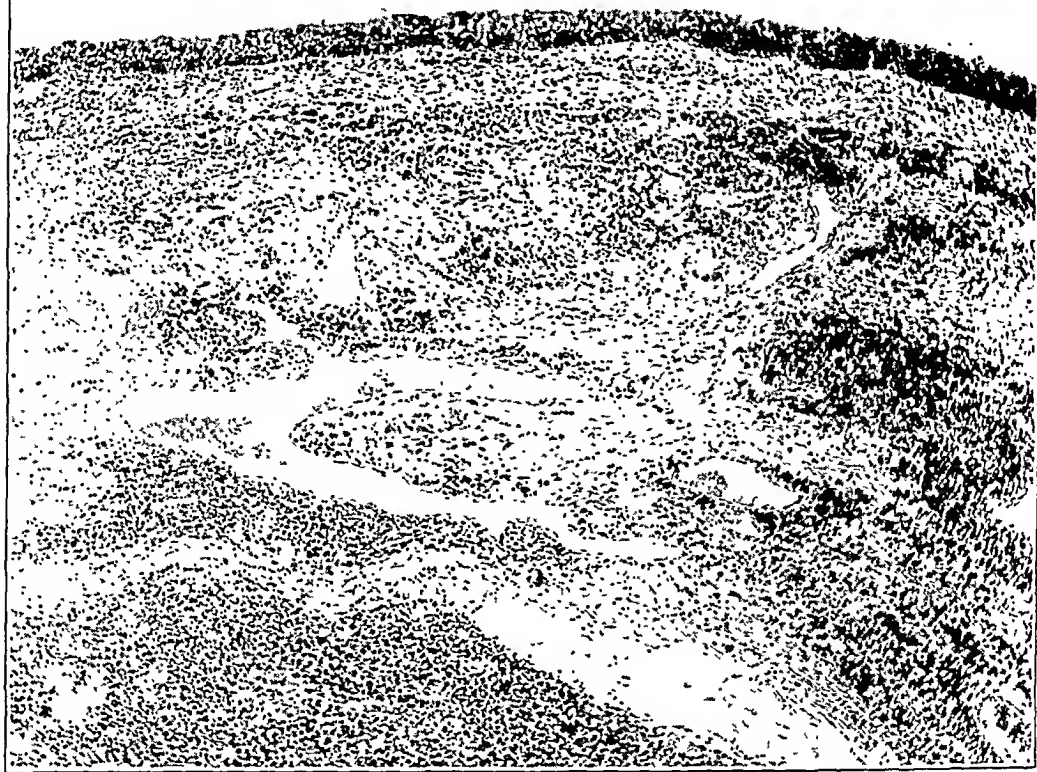


Fig. 3 (case 2).—Photomicrograph showing the plasma cell infiltration of the mucosa. Hematoxylin and eosin stain; $\times 70$.

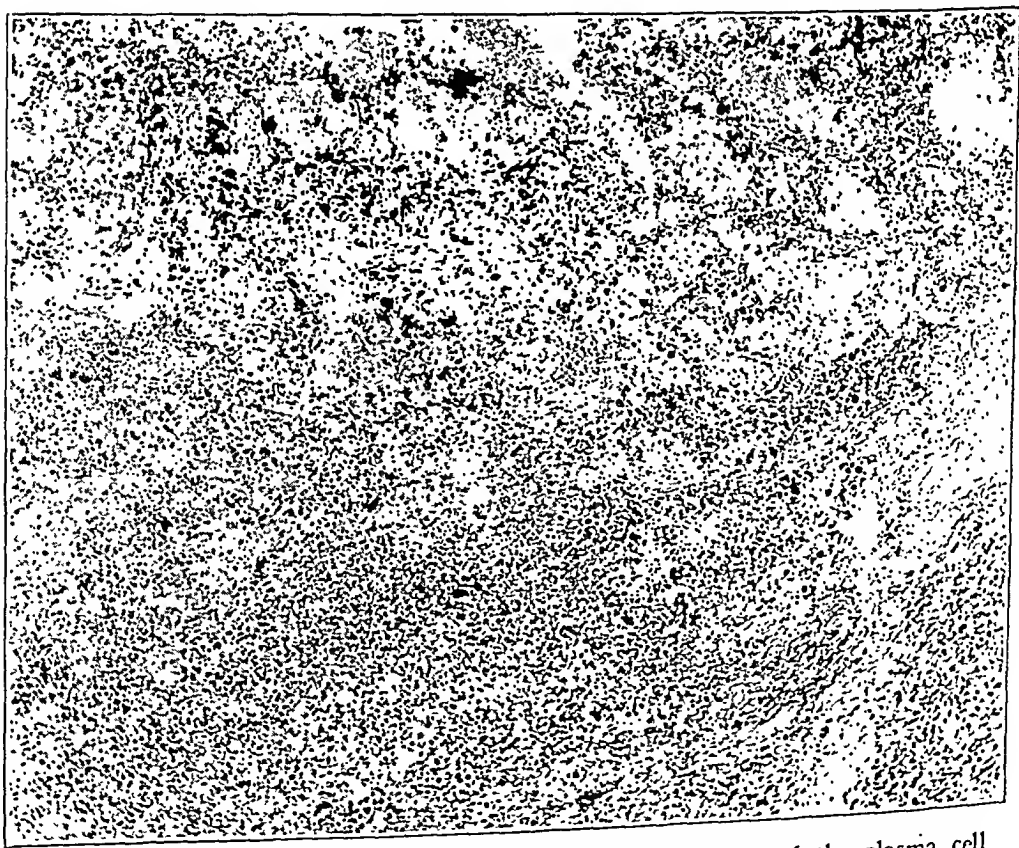


Fig. 4 (case 2).—Photomicrograph showing the density of the plasma cell accumulation with areas of hemorrhage in the upper portion of the plate. Hematoxylin-eosin stain; $\times 85$.

fibrous tissue in which numerous capillaries and blood spaces were seen. In this tissue, especially just beneath the surface epithelium, were a few scattered polymorphonuclear neutrophilic leukocytes. Scattered small round cells of the lymphocytic type were present and likewise plasma cells with abundant pink or gray homogeneous cytoplasm and rather dark, usually eccentrically placed nuclei. The latter, as a rule, showed a more densely arranged chromatin with less of the radial distribution than is usually found in these cells. Deeper in, the tissue consisted of large irregular masses of apparent plasma cells. These groups of cells were not sharply demarcated from the overlying mucosa, and in places extended irregularly in finger-like processes into that layer. The individual cells varied considerably in size and shape, some being only about two or three times the size of a lymphocyte, while others were many times that size. Where the cells lay free, they tended to be round or oval, but where they were found close together their outlines were frequently irregular. The cytoplasm had a grayish blue tint with hematoxylin-eosin stains. The nuclei were spherical, and in many cases eccentric in location. The chromatin in most nuclei formed little knotlike masses, the radial arrangement of which gave the nuclei the typical so-called cartwheel appearance. About a large number of the nuclei, the cytoplasm showed a clear semilunar zone, which has been frequently described as being present in plasma cells. Cells with two or even three nuclei, and rarely more, were seen, these cells usually being larger than the general average, but occasionally no greater in size. Throughout the sections were found scattered cells which corresponded in size and shape with the other plasma cells of the tumor, but which had pinkish-red, denser cytoplasm and usually darker, less typical nuclei. Where the plasmacytes were densely packed, the cell outlines were often indefinite, but a true sheetlike arrangement of the cells as often seen in carcinoma was not observed. The methyl green pyronin preparations did not show the nuclei of the cells to be stained green and the cytoplasm red, as is typical of plasmacytes, but this was probably due to the fact that the tissue was fixed in formaldehyde rather than alcohol. However, the general appearance of the cells, with their homogeneous cytoplasm, perinuclear clear zones and the radially arranged chromatin of the nuclei was typical of plasma cells, and leaves little doubt that they were of this nature. Moreover, the similarity of the cells in our cases to those described by other authors who successfully employed the Unna-Pappenheim stain, is extremely close. The stroma, as a rule, was slight, with only a few delicate strands separating the individual cells of the masses in most places. In other areas, fewer plasma cells were seen, and here the stroma was looser and showed spindle shape or oval connective tissue cells, small capillaries, and likewise numerous extravasations of red blood cells. No frank areas of necrosis were found. Lymphocytes were scattered among the plasma cells, but in a few places formed the predominant element. Mitotic figures in the plasmacytes were but rarely seen. Occasionally there were encountered large cells with several rather dark-staining nuclei, often irregular or bean-shaped. These cells did not in their appearance suggest plasma cells. Careful search was made for both spirochetes and acid-fast organisms in the sections prepared with the appropriate stains, but none was found.

Dr. Samuel Hammond of Hartford, gave us the clinical history of the first case and Dr. Wilmer Allen, pathologist of the Hartford Hospital, the pathologic material. Dr. Charles T. Fenn, assistant clinical professor of otolaryngology, Yale University School of Medicine, gave us permission to report the second case.

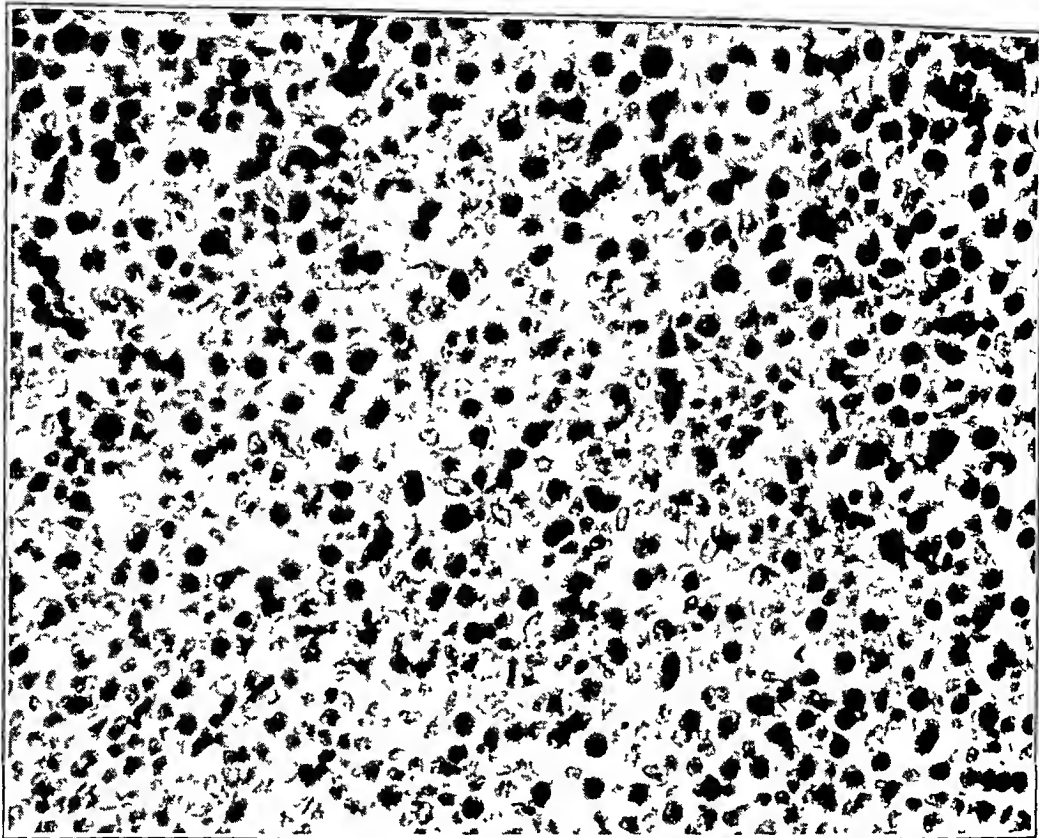


Fig 5 (case 2).—Photomicrograph demonstrating the type of plasma cells. The nuclei appear more darkly stained than they actually were Hematoxylin-eosin; $\times 300$.

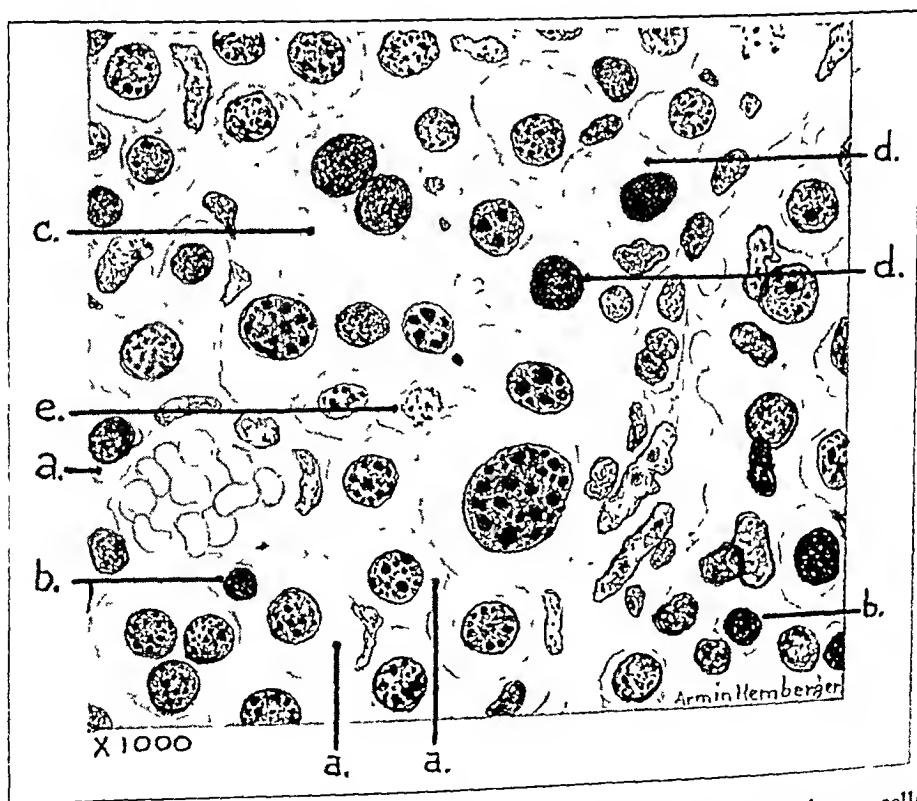


Fig. 6 (case 2).—Drawing showing the cellular detail: *a*, typical plasma cells; *b*, lymphocytes, *c*, multinucleated plasma cells; *d*, plasma cells with pyknotic nuclei and dark red staining cytoplasm; *e*, plasma cell with poorly defined nuclear membrane. Hematoxylin-eosin stain; $\times 1,000$.

Summary of Cases

Author	Date	Age	Sex	Symptoms, Duration, etc.	Location
Schridde ³	1905	40	M	Not given	Nose
von Werdt ⁴ ...	1911	69	M	Difficulty in swallowing and nasal speech; growth excised, and wound healed quickly with no recurrence	Posterior surface of uvula
Vogt ⁵	1912	20	M	Sudden onset of hoarseness, pain in neck; patient died before operation; necropsy done	Uvula, pharynx, tonsils, epiglottis, larynx, cervical, axillary and inguinal lymph nodes
Kusunoki and Frank ⁶ Frank ⁷	1913	44	M	Lump size of pea at angle of left jaw; two years later tumor in nasopharynx with respiratory difficulty; epistaxis, loss of weight; died four years after onset, showing swelling of upper part of thigh	Nasopharynx, left side of neck
Wachter ⁸	1913	48	F	Onset twenty years previous with slight hoarseness and pain in neck; operation; recurred locally; again removed; recurrence	Floor of right nasal fossa and inferior turbinate; floor of left nasal fossa; velum above uvula; left false vocal cord
Rogers ⁹	1920	42	M	Severe attacks of epistaxis for period of a year, nasal obstruction; growth removed; uneventful recovery	Inferior border of cushion of eustachian tube, and adjacent surface of soft palate
Facchini and Scalas ¹⁰	1925	47	F	For two years nasal obstruction; operation; no recurrence after a year	Right nasal cavity from posterior portion of septum
Rössle ¹¹	1926	54	M	Nasal obstruction; extirpation of tumor filling nasopharynx; death several days later; necropsy	Tumor grown through clivus, filled sphenoidal sinus; roof of pharynx involving upper part of left nose; posterior surface of soft palate; mucosa of left antrum of Highmore; cervical nodes, sternum, ribs, skull
Hüchel ¹²	1927	46	M	Difficulty in nose breathing for six months with almost complete nasal obstruction	Nasopharynx and mucosa of posterior edge of wing of the vomer
Pallestrini ¹³ ..	1927	43	M	Nasal obstruction; nasal discharge; frontal headaches; pain in region of the distribution of first and second divisions of the fifth nerve, right	The inferior half of the right lateral wall of nose
Bronzini ¹⁴	1928	53	M	Nasal obstruction with mucopurulent discharge; frequent sneezing	Inferior turbinate, right
Borri ¹⁵	1928	56	M	Difficulty in eating solid food; nasal occlusion; operation; recurred locally; operation; recurrence; disappearance following antisyphilitic treatment; Wassermann test positive	Left nasal fossa; right palatine tonsil; posterior pharyngeal wall
Authors' case 1	1930	34	M	Nasal obstruction; tumor removed; no recurrence	Right nasal fossa filling the entire interturbinate space
Authors' case 2	1930	60	M	Obstruction to right nose of two years' duration; nasal discharge; small growth removed; considerable improvement for a short time; recurrence of tumor; tumor again removed; no recurrence to date	Right nasal fossa extending from the middle meatus over the middle turbinate; fossa of Rosenmüller

COMMENT

While the series of cases that we have collected is too small to justify any general conclusions as to the age and sex incidence in cases of the tumors described, it is interesting to note that of the fourteen cases, twelve occurred in males and only two in females. The youngest patient was 20 years of age, while the oldest was 69. Of the fourteen patients, twelve were 40 years or more of age. The predominant symptoms that caused the patients to seek medical care were nasal obstruction (eleven cases); difficulty in deglutination (two cases); epistaxis (two cases), and hoarseness (two cases). In the instances in which hoarseness was a chief complaint the patients were found to have tumors in the pharynx as well as in the nasal or nasopharyngeal regions. Several patients complained of more than one of the foregoing symptoms. In summarizing the cases according to anatomic location, we found that five occurred in the nose alone; one in the nasopharynx; while in two instances both these sites were involved. In some instances tumors were also present in the oropharynx, larynx, lymph nodes or other sites.

Morphologically, the tumor masses were characterized grossly in the majority of the cases by a coarsely nodular or more finely granular appearance. They varied in size from those which almost or entirely filled the nasal or nasopharyngeal cavities to smaller masses from 1 to 3 cm. in diameter. Some had flat bases, while others were definitely pedunculated. The majority of the masses were firm. In our second case, however, the tumors were soft. The color was pale or pale gray, bluish red or dark brown, apparently resulting from congestion and hemorrhage. The latter was noted definitely on gross examination in three or four instances. Microscopically, all of the tumors were marked by the abundance of undoubted plasma cells. In only one or two instances were these described as being uniform in size and shape. More frequently they showed a good deal of variation in those respects, and cells containing two nuclei were commonly noted. Plasmacytes with more than two nuclei, the so-called plasma giant cells, were not infrequently observed. The nuclei were usually round or oval with radially arranged masses of chromatin. Multinucleated giant cells of the Langhan's type were seen by only one observer (Vogt⁵). Degenerated cells were described by only one or two authors. An obvious necrosis involving the plasma cells and interstitial tissue was not a frequent observation, but was mentioned by Frank.⁷ Hemorrhage was observed microscopically in those tumors in which it was manifest grossly. A particular abundance of capillaries was noted by some, and others found that the plasma cell groups were especially numerous in the vicinity of the blood vessels, often forming perivascular collars.

An almost universal observation was the delicacy of the interstitial connective tissue which formed a fine reticulum in which the plasma cells rested in rather closely packed masses. Denser trabeculae were observed in only a relatively few instances. Lymphocytes were quite numerous according to some descriptions, at times dominating the picture in small areas. Other observations of less frequency were the presence of rare mitotic figures and of eosinophils (one case). Polymorphonuclear neutrophilic leukocytes observed in both of our cases were in the second restricted to the mucosa covering the tumor, and formed no part of the masses rich in plasma cells.

In regard to these plasma cell tumors, the much debated question arises as to whether they are true neoplasms, or whether they have an inflammatory origin. Moreover, if the former is true, should they be considered as benign or malignant; and if the latter, is there a specific infectious agent, or is the inflammatory etiology unknown? In this discussion we will not enter the controversy as to the origin of plasma cells. It may be stated, however, that there are two main theories. One is that the plasma cells are derived from lymphocytes, the other that they come from the fixed tissue (the fibroblasts of the adventitia of the blood vessels). The first view is the one most commonly held.

Wachter⁸ considered that his case was to be classified from the clinical picture in the group of localized benign tumors, although the same plasma cell forms were seen as those described in the cases which were considered by other authors to be malignant. He believed that there was no pathologic evidence for considering it as having a chronic inflammatory basis. The same attitude was manifested by Facchini and Scalas¹⁰ in their discussion of the growth which they described. That such a structure could be a fibromyxoma with an infiltration of plasma cells was admitted, but they were of the opinion that their case lacked the evidences of chronic inflammation and of a granulomatous nature, the chief rôle being played by the cellular elements. The explanation of the etiology on a syphilitic basis was ruled out, they believed, by the repeatedly negative Wassermann tests and lack of specific clinical history and physical signs. Moreover, the epithelioid cells, lymphocytes, fibroblasts, foci of caseous necrosis and of sclerosis usually found in syphilitic processes were wanting, as well as a lack of evidence of endarteritis obliterans and other vascular changes. That a neoplasm of plasma cells could take origin from the nasal mucosa was thought by them to be explainable, as it had been demonstrated by others that numerous plasma cells exist in the normal mucosa. What factors might cause these plasma cells to multiply in such a manner as to form a neoplasm, they realized was difficult to determine,

and a discussion regarding their nature would lead one into the difficult field of the general etiology of tumors. They called especial attention to the fact that a year following the removal of the tumor there was no evidence of recurrence, and they therefore considered that their case was an example of a benign plasmacytoma, as opposed to most of the other cases described, which originated in the bone marrow or lymphatic glands and gave rise to metastases to other parts of the skeleton or even to the mucosa. Facchini and Scalas concluded that plasmacytomas of the nasal mucosa are often of benign nature. Hückel¹² felt likewise that in his case the description justified the classification of the plasma cell tumor as a new growth as opposed to a simple reactive cellular infiltration.

Among those cases which were definitely considered to be of a malignant nature, that of Rössle⁹ is outstanding. He concluded that the tumor which he described was unquestionably malignant on the basis of its invasive character. Rössle questioned whether in such tumors metastases to mucous membranes could occur through implantation. In this instance it was doubtful as to whether the point of origin was the mucosa or the bony posterior wall of the nose. He suggested that a malignant plasmacytoma is not so rare as generally believed, and perhaps in some instances has been unrecognized. Von Werdt⁴ believed that the plasma cell tumor described by him could be called a new growth because of its circumscribed form, the type and number of the cells, and the relation to blood vessels, and stated that it belonged to the group of sarcomas. He called it a plasmacytoma. Pallestrini¹³ believed that his case, which was unquestionably malignant (as shown by its course), should not be called a plasmasarcoma. He preferred to classify it as an atypical and malignant plasmoma to stress better the derivation and structure of the neoplasm. Vogt⁵ considered that his case was a neoplasm which had metastasized to the lymph nodes. In his conclusions, however, he termed it a plasma cell granuloma and suggested that possibly the etiologic agent was an "unknown noxious one."

An inflammatory origin for the masses of plasma cells was advanced by Borri.¹⁵ He believed that one must admit that with a general infection of long duration, such as tuberculosis or syphilis, there is a tendency toward a defense reaction characterized by the production of plasmacytes. He considered both of his cases to have a syphilitic basis. In these tumors the character and type of the cellular elements were, in his opinion, not indicative of a true neoplasm. He gave these tumors the name of "granuloma plasmacellulare" as did Vogt, who perhaps employed that term inadvisedly since he had previously called the condition a neoplasm with metastases.

Still other writers, after discussing various possible ways of grouping the tumors, reach no definite conclusions. Schridde³ stated that his case could not be considered a myeloma (malignant plasmoma) since tests for albumose in the urine were negative, and other evidence for this diagnosis was lacking. He expressed no definite views as to its nature. Kusunoki and Frank⁶ gave their tumor the name of plasma cell granuloma, which they believed was due to an unknown toxic agent acting on the vessel walls causing a transmutation of the fibroblasts of the adventitia to plasma cells. Frank,⁷ in a subsequent article discussing the same case, outlined arguments for and against the diagnosis of the tumor as a true neoplasm, a "leukemic-pseudo-leukemic" mass, or a granuloma. The history and clinical course did not support the diagnosis of a true neoplasm. Also the absence of invasion, and the formation of plasmacytes from the adventitial cells, rather than from preexisting plasma cells, were, in his opinion, against that hypothesis. If one defines the "leukemic-pseudoleukemic" tumor formation as an hyperplastic disease of the hematopoietic system, he felt that his case could not be so considered since the plasma cells there were not derived from specific elements of the blood-forming organs. Arguments for the granulomatous nature, aside from the localization, were the similarity of the process in the cervical nodes and nasopharyngeal mucosa, the marked growth of the adventitial cells of the vessels with transition into plasma cells, the latter cells themselves, the richness of the capillary formation and the presence of necrosis and hemorrhage. In regard to the etiology in his case, he stated that no micro-organisms were found. Neither was there support from the clinical data nor the histologic signs for the diagnosis of tuberculosis or syphilis. In the case described by Bronzini,¹⁴ that author considered that he was dealing with a neoplasm which was either a plasmacytoma or granuloma plasmacellulare. He excluded plasmasarcoma because of the clinical course. Syphilis was excluded by the history, physical examination and negative Wassermann test. He believed that sufficient criteria for the diagnosis of the growth as a true neoplasm were not present and he therefore preferred to call it a granuloma.

Fairly numerous descriptions of plasma cell tumors that were located extramedullarily in other portions of the body than the nasal or nasopharyngeal mucosa have been made. Some of these masses were accompanied by similar involvement of bony structures, but others did not have this complication. We will outline here the views of several of the authors concerning these tumors, since many of them are similar to ours structurally and vary only in their different locations and perhaps clinical course. Among those who claimed a benign neoplastic nature

for the plasma cell masses was Boit,¹⁶ who wrote in 1907. He described an involvement of the false vocal cord by tumorous plasma cells, and stated that on histologic grounds the prognosis was unfavorable, since both of the plasma cell tumors which had been previously reported were of malignant nature. The lack of recurrence shown on examination several months following operation, however, suggested to him that possibly the plasma cell tumor was not malignant and perhaps bore the same relation to a malignant plasmacytoma that a lymphoma does to a lymphosarcoma. Hedinger,¹⁷ in 1911, described a plasmacytoma of the scalp which was combined with a malignant adenoma of the sweat gland. He felt that a long-standing inflammatory process caused the plasma cells to proliferate after the nature of tumor cells, until a definite large granulation plasmacytoma resulted. Kaufmann,² in discussing this case, stated that there are transitions from simple reactive infiltration to plasma cell granuloma, distinguished by marked cellular proliferation. Deutschmann¹⁸ claimed, however, that these growths are tumors only by exclusion, since the etiology of an inflammation cannot be determined.

A malignant nature was manifested in the case described by Hoffmann¹⁹ in 1904, in which masses of plasma cells were found in the skull, sternum, clavicle, vertebrae, rib and liver. Micheli,²⁰ also in 1904, reported a similar case in which, in addition to bone marrow masses, infiltration of the plasma cells was present in the liver and spleen. He considered this a plasma-cellular pseudoleukemia. In neither of these was there any involvement of the surfaces of the skin or of the mucous membranes. We are of the opinion that these were probably true multiple myelomas. Sternberg and Menne, cited by Kaufmann,²¹ believed that the case of Hoffmann should be separated from the true myelomas because of the metastases to the liver. However, actual metastases to internal organs in multiple myeloma are not uncommon. A careful review of cases made by Geschickter and

16. Boit, H.: Ein Fall von Plasmocytom des Sinus morgagni, Frankfurt. Ztschr. f. Path. **1**:172, 1907.

17. Hedinger, E.: Zur Frage des Plasmacytoms, Frankfurt. Ztschr. f. Path. **7**:343, 1911.

18. Deutschmann, F.: Das Plasmom, die hyaline und amyloide Degeneration der Konjunktiva, Ztschr. f. Augenh. **27**:242, 1912.

19. Hoffmann, R.: Ueber das Myelom, mit besonderer Berücksichtigung des malignen Plasmoms, Beitr. z. path. Anat. u. z. allg. Path. **35**:317, 1904.

20. Micheli, F.: Pseudoleucemia plasmacellulare, abstr., Folia haemat. **1**:440, 1904.

21. Sternberg and Menne, cited by Kaufmann, E.: Pathology, transl. by Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 2, pp. 1216-1222.

Copeland²² revealed rather numerous instances in which visceral metastases were reported. A case described by Maresch²³ showed plasma cell involvement of bone marrow, lymph nodes, spleen and liver. Here the tumors of the bone marrow were not prominent. He called this a plasma-cellular granuloma. It might well be considered, however, along with those of Hoffmann and Micheli as a multiple myeloma. Kaufmann²¹ recognized the occasional occurrence of nodular myeloma in various viscera which produce the picture of metastatic nodules, but he believed that typical myelomas are not malignant tumors and that these heterotopic masses are not true metastases such as occur in malignant neoplasms, but are merely an expression of a systemic disease of the hematopoietic apparatus. In this connection we might mention the case of Ghon and Roman²⁴ in which a diffuse plasma-cellular hyperplasia of the lymphatic hematopoietic system was found, analogous to changes seen in leukemia and pseudoleukemia. Practically all of the organs as well as the bone marrow showed a varying degree of infiltration of the plasma cells. In discussing a plasma cell tumor of the pleura, Klose²⁵ held that it was malignant, since it invaded the adjacent soft parts.

An inflammatory nature was suggested for a number of localized plasma cell tumors occurring in various sites such as the conjunctiva (Pascheff, Rados, Porkowsky, Franke and Baumann); the lip (Kaufmann); anus (Albrecht) and jaw (Pirone). These authors were cited by Hückel.¹² Baumann considered carefully the conflicting question of the etiology and nature of the tumors. He maintained that the criteria advanced by Boit and von Werdt to support their diagnosis of plasmacytomas as benign tumors were not in any sense conclusive. He also rejected Deutschmann's claim that the diagnosis of tumor was made only by exclusion, and held that it is justifiable to consider accumulations of plasma cells as an anatomic evidence of inflammation. Alagna,²⁶ who made a rather extensive study of nasal polyps, divided them into two groups, which he called the serous and granulomatous. Definite structural differences were noted. In the serous type, a watery stroma, often cystic, was present, with only scattered cellular elements

22. Geschickter, C., and Copeland, M.: Multiple Myeloma, *Arch. Surg.* **16**: 807 (April) 1928.

23. Maresch, R.: Ueber ein plasmazelluläres Lymphogranulom, *Verhandl. d. deutsch. path. Gesellsch.* **13**:257, 1909.

24. Ghon, A., and Roman, B.: Ueber pseudoleukämische und leukämische Plasmazellen-Hyperplasie, *Folia haemat.* **15**:72, 1913.

25. Klose, H.: Ueber das Plasmocytom der Pleura, *Beitr. z. klin. Chir.* **74**:20, 1911.

26. Alagna, G.: Die Plasmazellen bei Ohren-Nasen und Kehlkopfkrankheiten, *Virchows Arch. f. path. Anat.* **204**:135, 1911.

such as lymphocytes, neutrophilic polymorphonuclear cells and plasmacytes. In the granulomatous form, the polyps consisted of a structure identical with granulation tissue. In these the plasma cells were the predominant element, and in places they were so closely packed that it was difficult to find other types of cells. He believed that this type occurred only associated with infections of the nasal sinuses. He further suggested that the formation of true plasmomas from the granulomatous polyps may result from the continuous irritation of the secretions from the diseased sinuses. An association with syphilis was pointed out by Bunger (quoted by Hückel¹²), who mentioned a case of primary syphilitic infection (spirochetes demonstrated) in which a diagnosis based on the microscopic signs of plasmacytoma was previously made by a competent observer. More recently, di Vestea²⁷ described a massive plasma cell involvement of both tonsils in an 82 year old man. The patient's Wassermann reaction was strongly positive, and the lesions disappeared following treatment with sodium caccodylate and mercury. He stated that in the simple hypertrophic form of syphilitic tonsillitis, a transition may take place to a plasmomatous hypertrophic form which represents a true neoplastic tissue of a specific inflammatory type. He quoted di Donato to the effect that the plasma cell elements must be considered above all as an exponent of syphilitic specificity when their number is such that a true plasmomatous mass is constituted. Unna (cited by Hückel¹² and Ghon and Roman²⁴ and others), who was the first to use the expression plasmacytoma in 1891, described plasma cells as specific elements for lupus and other tuberculous processes of the skin. Since then, however, these cells have been found in other inflammatory reactions and in many normal organs.

In regard to our cases, we believe that the evidence that our first case was neoplastic is not convincing. The infiltration of leukocytes in the tumor itself is marked. Moreover, the plasma cells are more typical in appearance than those seen in the second case. The structure in all suggests an inflammatory rather than a neoplastic nature. It is true, however, that we have no proof of an etiologic agent. We were unable to employ the special stains used for the demonstration of micro-organisms. In the second case, we could find neither spirochetes nor tubercle bacilli. This, of course, of itself, does not rule out a syphilitic or tuberculous origin. The history and clinical signs do not, however, suggest such a causation of the lesions. The marked variation in size and shape of the plasma cells with the many giant forms, often multinucleated, we believe is evidence of a neoplastic nature. Aside

27. di Vestea, D.: *Plasmoma tonsillare e angina sifilitica*, *Valsalva* 4:448, 1928.

from an occasional double nucleated plasma cell, we have not observed this great variation in inflammatory infiltration of the plasma cells. The fact that plasma cell tumors of the bone (multiple myeloma), which our second case somewhat resembles in histology, are probably malignant tumors, suggests that the localized growths are likewise at least neoplasms. It may be objected by some oncologists that the instances with apparent location of the tumor only in the mucous membranes, are really cases of multiple myeloma, in which the bony involvement has not been demonstrated by necropsy or thorough roentgen study. In our second case there was no roentgenologic evidence of bony involvement of the skull. In neither case were there clinical signs to suggest a bony involvement locally or elsewhere. It is extremely unlikely that a single metastatic growth in the mucosa of medullary origin could be present for at least two years without other clinical manifestations of the tumor process in the skeleton, viscera or elsewhere.

The localized nature, the general architecture and the cellular structure with absence of numerous mitotic figures indicate to us that the tumors in our second case should be classified as benign neoplasms of unknown etiology, to which the term "plasmacytoma" may be applied. The tumor in our first case had indefinite neoplastic characteristics and was probably inflammatory.

SUMMARY AND CONCLUSIONS

1. Twelve cases of plasma cell tumors occurring in the nasal or nasopharyngeal mucosa have been reported in the literature. We have reviewed these and added two cases of our own. Of these, all but two occurred in men.

2. Plasma cell tumors of the nasal and nasopharyngeal mucosa are probably much more frequent than the specific literature would lead one to believe. Undoubtedly many growths diagnosed clinically as nasal polyps and not studied microscopically have a predominant plasma cell structure.

3. Accumulations of plasma cells may accompany syphilitic, tuberculous or other chronic inflammatory processes to such a degree as to simulate true neoplasms.

4. Many of the plasma cell tumors are benign neoplasms. Most of the cases that appear malignant are probably manifestations of multiple myelomas.

OBSTRUCTIVE PULMONARY ATELECTASIS

FURTHER STUDIES *

W. E. ADAMS, M.D.

AND

H. M. LIVINGSTONE, M.D.

CHICAGO

In a recent publication ¹ on the subject of obstructive pulmonary atelectasis, two etiologic factors were described as being essential to its production, viz., bronchial obstruction and labored respiration or expiration against resistance. The latter of these two factors was contrary to the observations of Lee,² Coryllos and Birnbaum³ and others,⁴ who had produced the condition experimentally with regularity, and who believed a quiet, shallow respiratory cycle to be one of the important factors in its etiology. This idea has been carried down from the time of Pasteur⁵ who, observing several cases of massive atelectasis associated with postdiphtheritic paralysis of the diaphragm, believed it due to a reduction in the depth of respiration.

When an attempt was made to reproduce the results of other investigators, the factor of straining respiration was accidentally encountered and massive atelectasis produced with routine regularity in its presence.

That straining respiration was an essential factor in the production of massive atelectasis was made more evident, unfortunately, by several experiments⁶ in which there was complete stenosis of a bronchus for a period of weeks or months under normal living conditions with no

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1. Van Allen, C. M., and Adams, W. E.: *The Mechanism of Obstructive Pulmonary Atelectasis*, *Surg. Gynec. Obst.* **50**:385, 1930.

2. Lee, W. E.; Tucker, G.; Radvin, I. S., and Pendergrass, E. P.: *Studies on Experimental Atelectasis*, *Ann. Surg.* **88**:15, 1928; *Experimental Atelectasis*, *Arch. Surg.* **18**:242 (Jan.) 1929.

3. Coryllos, P. N., and Birnbaum, G. L.: *Obstructive Massive Atelectasis of the Lung*, *Arch. Surg.* **16**:501 (Feb.) 1928.

4. Henderson, Y.: *The Physiology of Atelectasis*, *J. A. M. A.* **93**:96 (July 13) 1929.

5. Pasteur, W.: *Am. J. M. Sc.* **100**:242, 1890.

6. Adams, W. E., and Livingstone, H. M.: *Bronchial Injury and Repair*, *Ann. Surg.* **91**:342, 1930.

resulting atelectasis. This appeared to be striking evidence that forced respiration was essential to the production of this condition. That this evidence was false will be brought out in the experiments to be described in this paper.

In more recent investigative work⁷ dealing with the reparative processes of bronchi following injury, it was found that complete stenosis of a bronchus resulted from cauterization with a solution of silver nitrate. Much to our surprise, the total obstruction of the air passage was accompanied by massive atelectasis of the lobe of the lung. This was the stimulus for the following experimental work.

EXPERIMENTAL WORK

Our previous experiments entailed the use of an artificial obstruction to the air passages and proceeded in a manner by no means comparable to that in which massive atelectasis is produced clinically. The following experiments made use of an obstruction and mechanism that were entirely physiologic in the production of their results.

Dogs were used exclusively. Their weights ranged from 11 to 14 Kg. Morphine, 0.015 Gm. per kilogram of weight and atropine, 0.0004 Gm. per kilogram, were administered from one to one and one-half hours before bronchoscopy. No other form of anesthesia was employed. The experiments were terminated by electrocuting the animals,⁸ thus avoiding agonal phenomena. The lungs were examined grossly, microscopically and roentgenologically.

The experiments were divided into three groups. The first two groups dealt with the location of the obstruction in the air passages. The third group had to do with the rôle played by respiration.

Typical protocols are as follows:

PROTOCOL 1 (dog 366 B).—*Obstruction located in the primary bronchus of a pulmonary lobe (obstructing the entire lobe).*

This animal was cauterized by the application of a 50 per cent solution of silver nitrate for ten seconds to the origin of the bronchus of the right middle lobe, and was killed two weeks later. Complete stenosis of the primary bronchus of the right middle lobe with 100 per cent atelectasis resulted.

Feb. 20, 1930: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.004 Gm. of atropine was given by hypodermic injection. With the dog secured in a dorsal position and a gag inserted in its mouth, a bronchoscope was introduced and carried down to the right primary bronchus. The origin of the bronchus of the right middle lobe was located and a cotton applicator saturated with a 50 per cent

7. Adams, W. E., and Livingstone, H. M.: Further Studies in Bronchial Injury and Repair, to be published.

8. Hrdina, L. S.: Electrocutation in Sacrificing Laboratory Animals, J. Lab. & Clin. Med. 15:86, 1929.

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solution of silver nitrate introduced into it and allowed to remain for ten seconds. After removal of the cautery, the bronchial wall appeared corroded. The dog was then placed in its cage, still in a stuporous state.

February 21: The dog was very quiet, appeared ill and did not eat. It did not cough or bark.

February 22: The dog appeared the same; however, an occasional nonproductive cough was noted.

February 23: The dog was much better. It ate some, but the cough was still present.

February 24: The dog appeared normal except for an occasional nonproductive cough.

February 25: There was no cough on this date.

February 27: The dog appeared healthy and normal.

March 5: Bronchoscopy was carried out as before. The origin of the bronchus of the right middle lobe was found to be completely stenosed.

March 6: The animal was electrocuted.

At autopsy, the bronchus of the right middle lobe was found to be completely stenosed over a distance of 0.75 cm. The right middle lobe was 100 per cent atelectatic. It was dark bluish red, flabby in consistency and would not float when placed in water (figs. 1 and 2). Microscopic sections verified the diagnosis made from the gross examination (figs. 3 and 4). The larger air passages were dilated and filled with a mucogelatinous substance, the retained secretions of the mucous glands. The smaller air passages were completely collapsed (figs. 5 and 6).

The results of thirty experiments comparable to protocol 1 were identical in every way. The number of applications of the cauterizing agent necessary to produce complete stenosis of the air passages varied from one to three, depending on the diameter of its lumen. Also the length of time consumed in producing complete stenosis varied from one to six weeks, depending on the diameter of the bronchus and also on the per cent of solution used in cauterization. A more detailed study of this will appear in a subsequent publication.⁷

If at autopsy the primary bronchus of a lobe was found to be completely stenosed, this condition was accompanied by massive atelectasis (100 per cent) of the obstructed pulmonary lobe. However, if the stenosis was all but complete, with an opening of only 1 mm. remaining, no atelectasis resulted. The lobe appeared normal both on gross and on microscopic examination.

PROTOCOL 2 (dog 213 B).—*Obstruction located in secondary bronchus of a pulmonary lobe (obstructing only a part of lobe; one-half or three-fourths).*

This animal was cauterized by the application of a 35 per cent solution of silver nitrate for ten seconds to the bronchus of the right lobe, just distal to the origin, and was killed two weeks later. Complete stenosis of only one of two main divisions of the primary bronchus of this lobe occurred, but no atelectasis resulted.

March 13, 1930: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.005 Gm. of atropine was given by hypodermic injection. With the animal in a dorsal position with a gag inserted in its mouth, a bronchoscope was introduced and carried

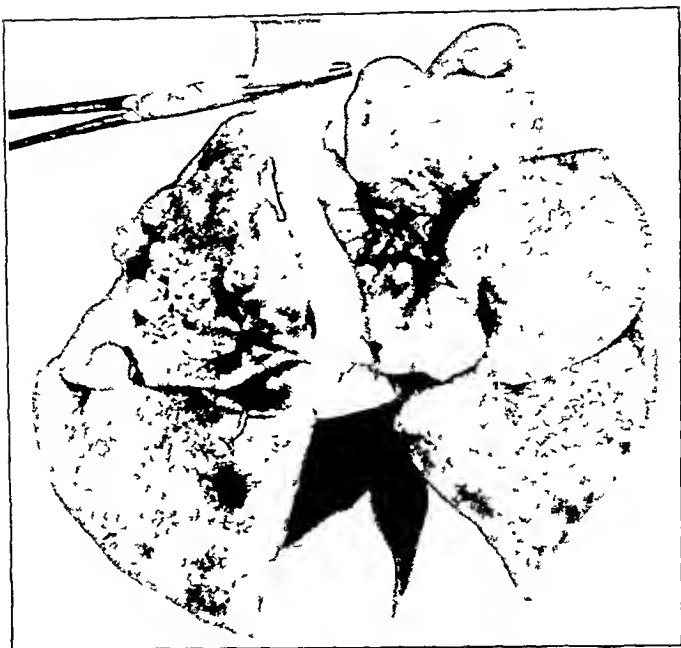


Fig. 1 (dog 486C) —Massive atelectasis of the accessory lobe of the lungs of one week's duration, following complete stenosis of the primary bronchus with 15 per cent solution of silver nitrate.



Fig. 2 (dog 641C).—Massive atelectasis of entire left lung of two weeks' duration, following complete stenosis of the left primary bronchus with 35 per cent solution of silver nitrate.

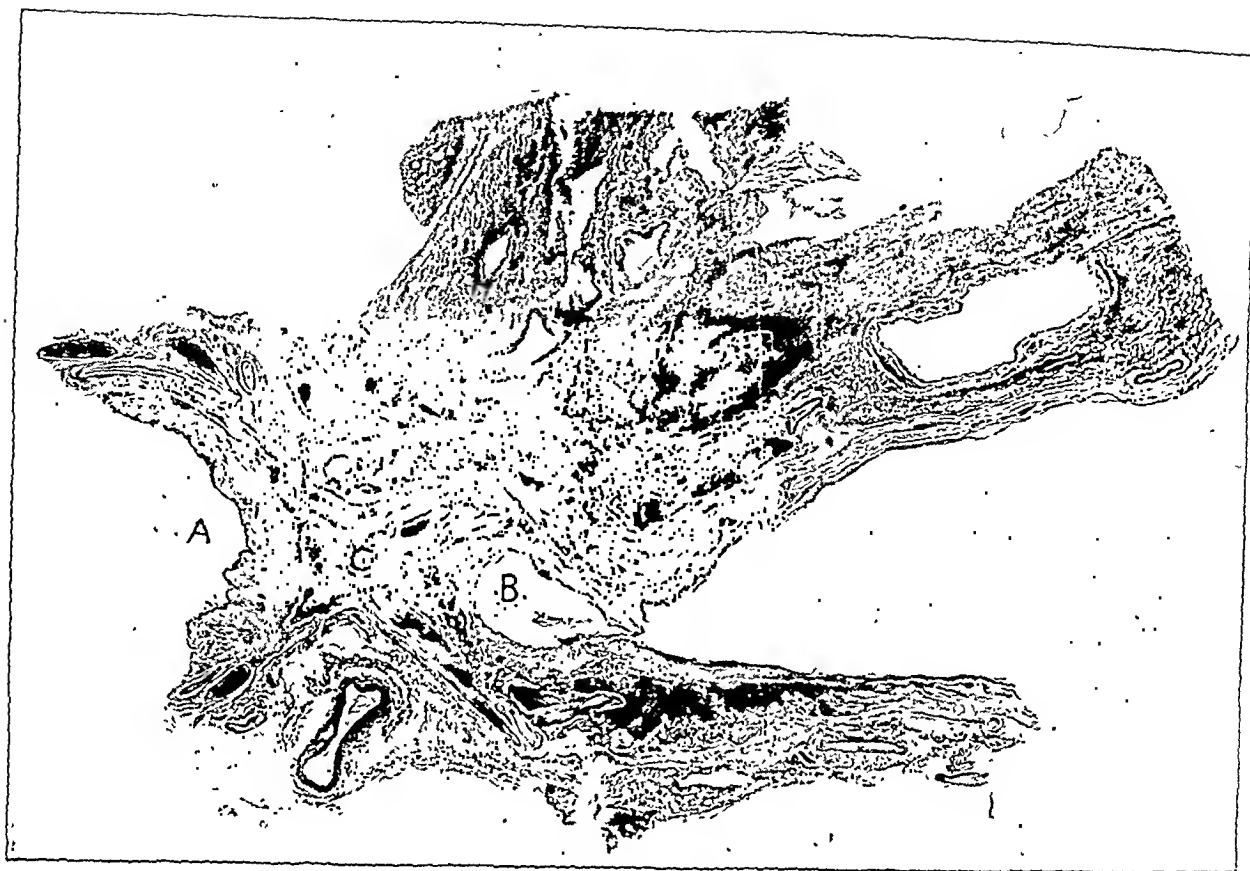


Fig. 3 (dog 365B).—Microscopic appearance of stenosed primary bronchus of a pulmonary lobe two weeks following cauterization with 50 per cent solution of silver nitrate. *A* indicates the origin of the primary bronchus of the lobe and the proximal side of the stenosis; *B*, the distal side of the stenosis. Reduced from a magnification of $\times 7$.



Fig. 4 (Dog 365B).—Higher magnification of the area indicated by *C* in figure 3. Note the partially destroyed cartilage plates intermingled with fibrous tissue, with complete regeneration of the bronchial epithelium on either side of the stenosis. Reduced from a magnification of $\times 30$.

to the right primary bronchus. The origin of the bronchus of the right lower lobe was located, and a cotton applicator saturated with a 35 per cent solution of silver nitrate was introduced into it to the level of division of the primary into the several secondary bronchi. It was allowed to remain for ten seconds. After removal of the cautery, the bronchial wall appeared encircled by an area of corrosion. The dog was then placed in its kennel, still in a drowsy condition.

March 14: The dog was quiet. It did not eat or bark, and appeared somewhat ill, but would walk around.

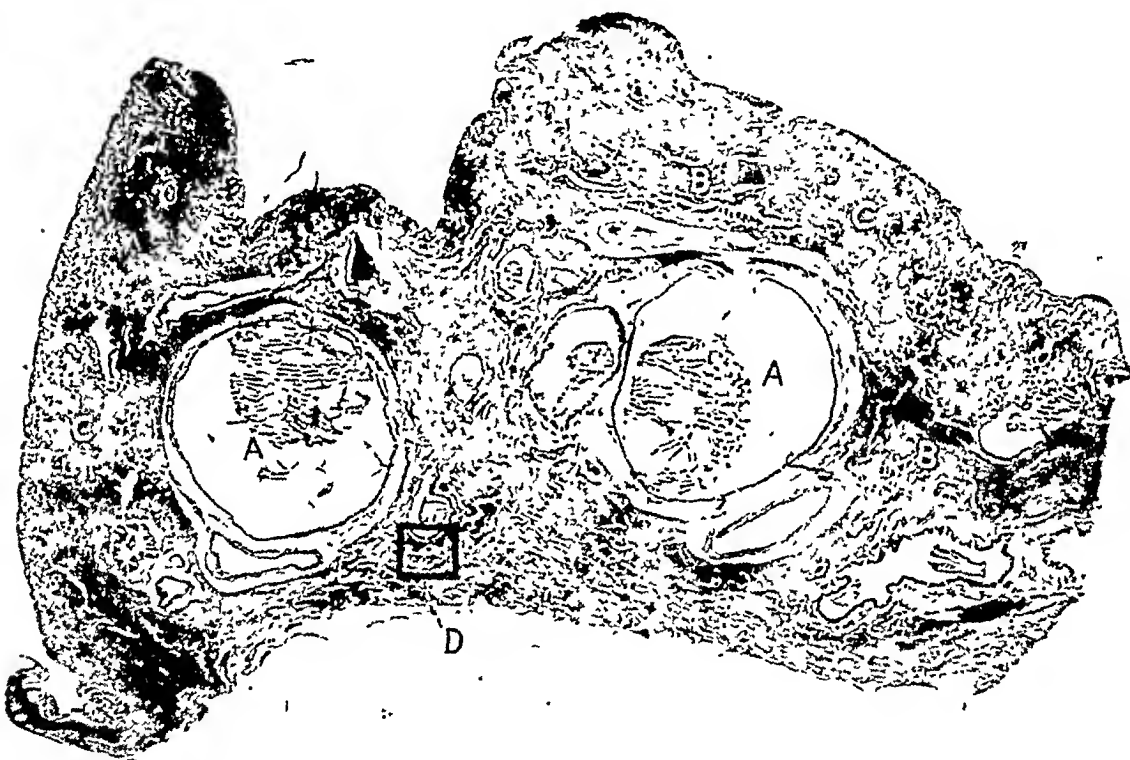


Fig. 5 (dog 365B).—Microscopic appearance of an atelectatic lung distal to a completely stenosed primary bronchus of three weeks' duration following cauterization which was done with 50 per cent solution of silver nitrate. *A* shows the dilated larger air passages filled with mucoid material (this entirely filled the lumen of the air passages before fixation); *B*, collapsed smaller air passages, and *C*, atelectatic parenchyma. Reduced from a magnification of $\times 9$.

March 15: There was little change in the animal's condition.

March 16: A nonproductive cough was occasionally noted. The dog ate some food, but was quiet.

March 17: The dog was very well except for an occasional nonproductive cough.

March 18: A slight cough was present.

March 20: The dog appeared healthy and normal.

March 26: Bronchoscopy was repeated. The primary bronchus of the right lower lobe presented an opening about 1 or 2 mm. in diameter.

March 26: The dog was electrocuted.

At autopsy, the lateral secondary bronchus to the lower right lobe was completely stenosed, with the air passages distal to the stenosis dilated and filled with a mucogelatinous material, the retained secretion from the mucous glands. The medial secondary bronchus was markedly but not completely stenosed, an opening of 1 or 2 mm. remaining. There was no dilatation distal to this incomplete stenosis. The entire lobe was normally air-containing on external examination and on cut

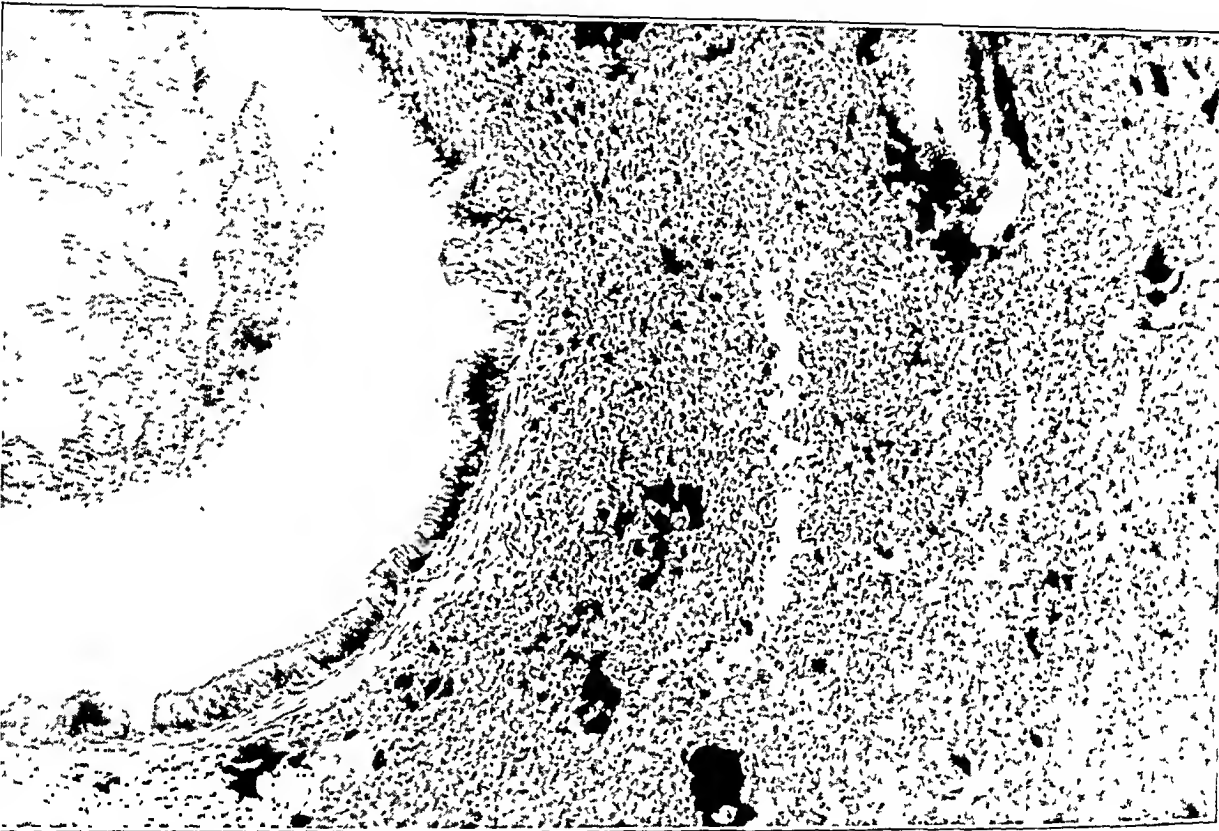


Fig. 6 (dog 365B).—Higher magnification of area indicated by *D* in figure 5. Note the dilated bronchus surrounded by atelectatic parenchyma and filled with mucoid material. Reduced from a magnification of $\times 175$.

section. Pieces floated on the surface when placed in water. Microscopic section showed the alveoli to be air-containing (figs. 7, 8 and 9).

The same results were obtained in ten experiments, protocol 2 being typical of this series. Various lobes of the lungs were used, like results being obtained with regularity. The duration of the experiments was also varied from two weeks to two months with no alteration in the end-results. Thus, complete obstruction to the air passages of only a part of a lobe was not followed by massive collapse. Only a dilatation of the larger air passages distal to the stenosis resulted, with the alveoli normally air-containing.

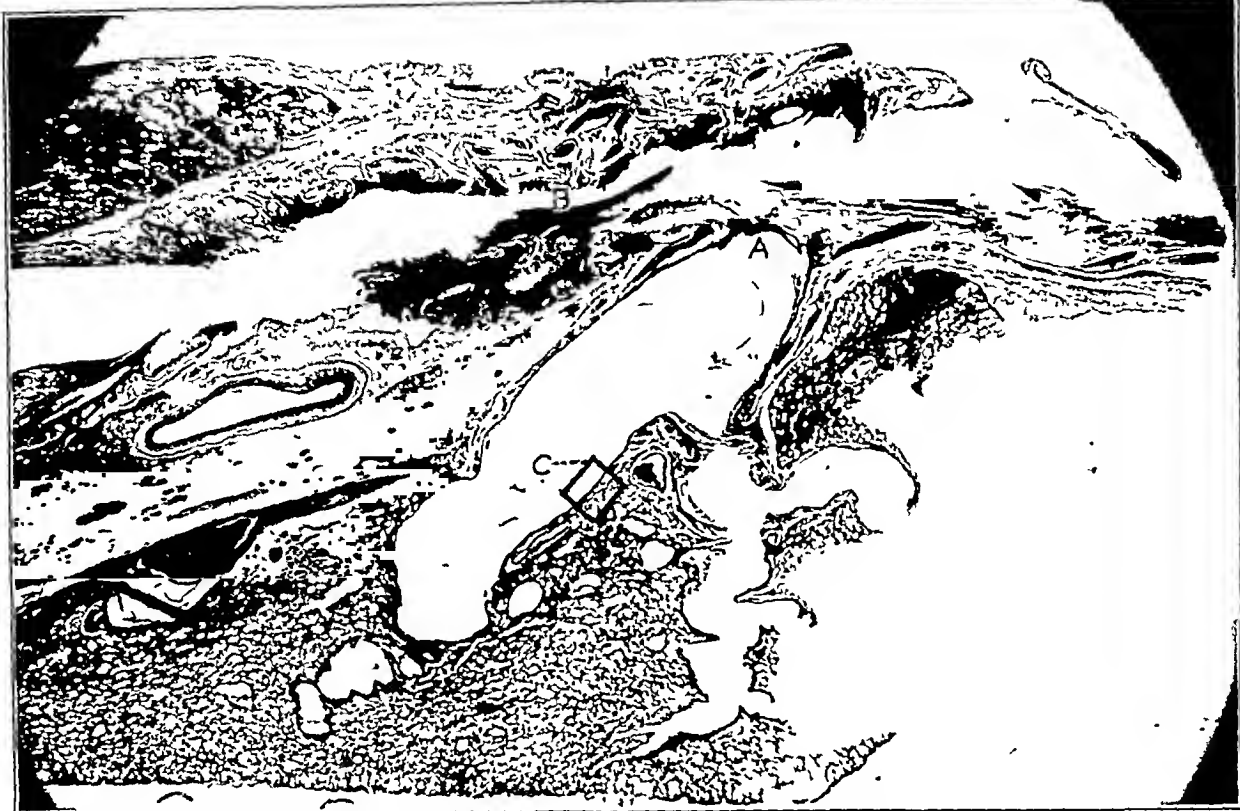


Fig. 7 (dog 213B).—Microscopic appearance of complete stenosis of secondary bronchus of a lobe of the lung and partial stenosis of remainder of air passage two weeks following cauterization with 35 per cent solution of silver nitrate. *A* shows complete stenosis with dilatation of air passage distal to the stenosis. Reduced from a magnification of $\times 6$.



Fig. 8 (dog 213B).—Higher magnification of area *A* in figure 7 showing fibrous tissue septum and regenerated bronchial epithelium on distal side of stenosis. Reduced from a magnification of $\times 120$.

The factor of respiration in the production of massive atelectasis has been greatly discussed by the many writers on this subject. The following six experiments were carried out to determine if a certain type of respiration was essential to the production of this condition.

PROTOCOL 3 (dog 661 C).—*Total obstruction of an entire pulmonary lobe in the presence of normal respiration.*

This dog was cauterized by the application of a 35 per cent solution of silver nitrate for ten seconds to the origin of the bronchus of the accessory lobe, and



Fig. 9 (dog 213B).—Higher magnification of area C in figure 7 showing dilated bronchus surrounded by normally inflated alveoli. Reduced from a magnification of $\times 85$.

killed two weeks later. Complete stenosis of the primary bronchus of the accessory lobe with 100 per cent atelectasis of this lobe resulted.

May 20: A prebronchoscopic dose of 0.15 Gm. of morphine and 0.004 Gm. of atropine was given by hypodermic injection. With the dog lying in a dorsal position and a gag inserted in its mouth, a bronchoscope was introduced and carried down to the right primary bronchus. The origin of the bronchus of the accessory lobe was located and a cotton applicator saturated with 35 per cent solution of silver nitrate introduced into it and allowed to remain for ten seconds. After removal of the cautery, the bronchial wall presented an area of corrosion encircling the lumen. The dog was then placed in its kennel in a stuporous condition.

May 21, 1930: The animal was very quiet, appeared ill and refused food.

May 22: An occasional nonproductive cough was noted. The dog appeared ill, refused food and was quiet.

May 23: The dog was somewhat better, but was still quiet. It ate little, and the cough was still present.

May 24: The cough was still present; otherwise the dog was quite well. Its appetite was good.

May 25: The dog coughed less frequently, and seemed quite well.

May 27: The dog appeared healthy and normal.

June 10: The animal was electrocuted. (No bronchoscopy was done prior to electrocution.)

At autopsy, the primary bronchus of the accessory lobe was found completely stenosed for a distance of 0.75 cm. The accessory lobe was found to be 100 per cent atelectatic. It was bluish red and of the consistency of flabby muscle, and pieces sank readily when placed in water. The larger air passages were dilated and filled with a mucogelatinous material, the retained secretions of the bronchial mucous glands. The smaller air passages were completely collapsed. Microscopic sections verified the diagnosis made from the gross examinations.

Protocol 3 is typical of the six experiments of this type, similar results being obtained in each. Thus, a particular type of respiration is unessential for the production of massive collapse, as it occurs in the presence of normal respiration.

The association of massive collapse and pneumonia has recently received much attention.⁹ It is the opinion of some¹⁰ that massive atelectasis is a precursor of pneumonia in a large percentage of cases.

In some recent investigative work,¹¹ it was found that the parenchyma of the lung of normal dogs was always infected with bacteria. In several of the foregoing experiments cultures were taken of the collapsed parenchyma of the lung. In each case the same organisms were cultivated as those found in the parenchyma of the lung of a normal dog. However, in no case of massive atelectasis was there associated any form of pulmonary suppuration. The pathogenicity of these organisms is being investigated at the present time.

COMMENT

It has been generally accepted among recent workers that the production of massive atelectasis is favored by the presence of a diminished respiratory effect. It is contended that this form of respiration leads to the collection and accumulation of secretions within the air passages.

9. Coryllos, P. N.: Postoperative Aponeumatoses and Postoperative Pneumonia, *J. A. M. A.* **93**:98 (July 13) 1929; Postoperative Pulmonary Complications and Bronchial Obstructions, *Surg. Gynec. Obst.* **50**:795, 1930.

10. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcal Lobar Atelectasis of the Lung: Bronchoscopic Investigation, *Arch. Surg.* **18**:190 (Jan.) 1929. Henderson, Y.: Acapnia as a Factor in Post-Operative Shock, Atelectasis and Pneumonia, *J. A. M. A.* **95**:572 (Aug. 23) 1930.

11. Livingstone, H. M., and Adams, W. E.: Bacterial Flora of the Lower Respiratory System of Normal Dogs, *J. Infect. Dis.* **48**:282 (March) 1931.

Thus with obstruction, atelectasis is produced by absorption of the imprisoned air by the blood. In our former experiments it appeared impossible to produce this picture in the presence of quiet respiration. However, an artificial means of obstruction was used, and experiments ran for only twenty-four hours or less. Our belief that a forced respiratory effort was an essential factor was unfortunately strengthened by several experiments in which the air passage to part of a lung was completely obstructed without resultant atelectasis. A like result has been described in a number of experiments. Thus, when the obstruction in the lung is located in such a manner that all of the lobe is affected, complete

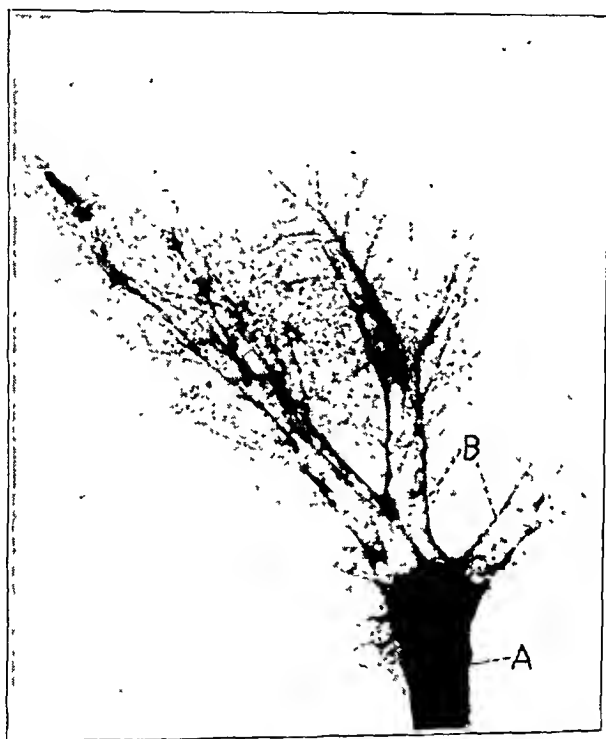


Fig. 10.—Roentgenogram of a dog's pulmonary lobe, to illustrate various locations in the air passages at which stenosis was produced. *A* shows the primary bronchus of the lobe of the lung, and *B*, the secondary bronchus.

atelectasis follows. However, if a small amount of the lobe (one-third, one-fifth, etc.) is left unobstructed, no atelectasis is produced (fig. 10).

It is the general belief that the lobules of a lobe of the lung are each a closed system in themselves. That is, there are no communications between the air passages of two or more adjacent lobules of a lobe. Indeed, the anatomy of the lung has been carefully studied by dissection under microscopic vision, resulting in the foregoing conclusion.¹² How-

12. Macklin, C. C.: *The Musculature of the Bronchi and Lungs*, *Physiol. Rev.* **9**:1, 1929. Reisseisen, F. D.: *Ueber den Bau der Lungen*, Berlin, 1822. Miller, W. S.: *Anastomosing Bronchi in Human Lung*, *Arch. Path.* **3**:161 (Feb.) 1927.

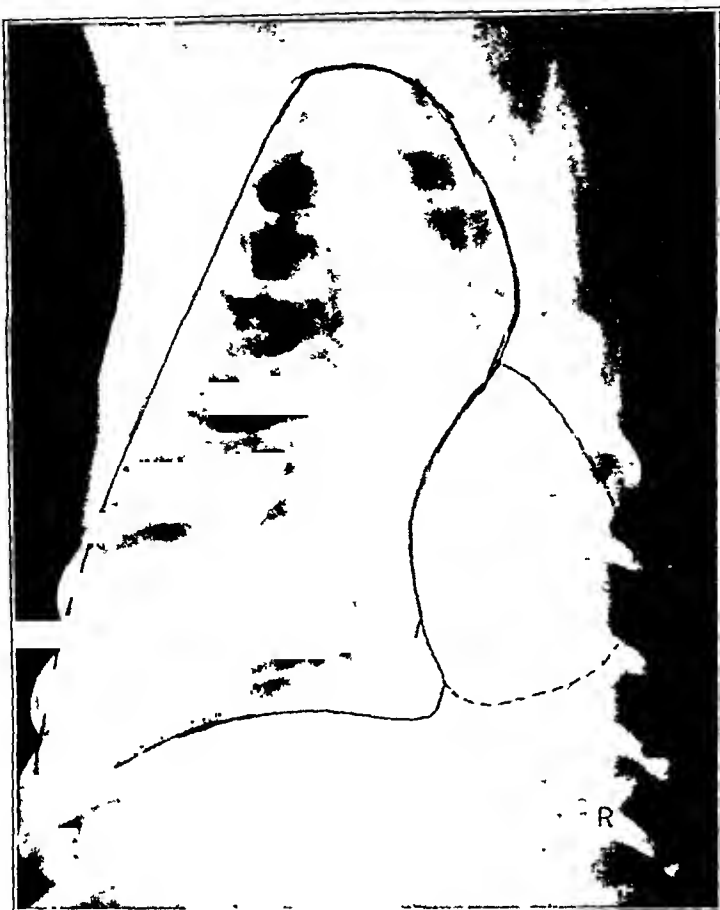


Fig. 11 (dog 610B).—Roentgenogram of the chest two weeks following cauterization of the right primary bronchus with 35 per cent solution of silver nitrate. Note the heart is drawn over against the right lower thoracic wall. (Autopsy showed massive atelectasis of entire right lung similar in appearance to that shown in figure 2.) Note the markings for the relative position of the heart and the left lung.

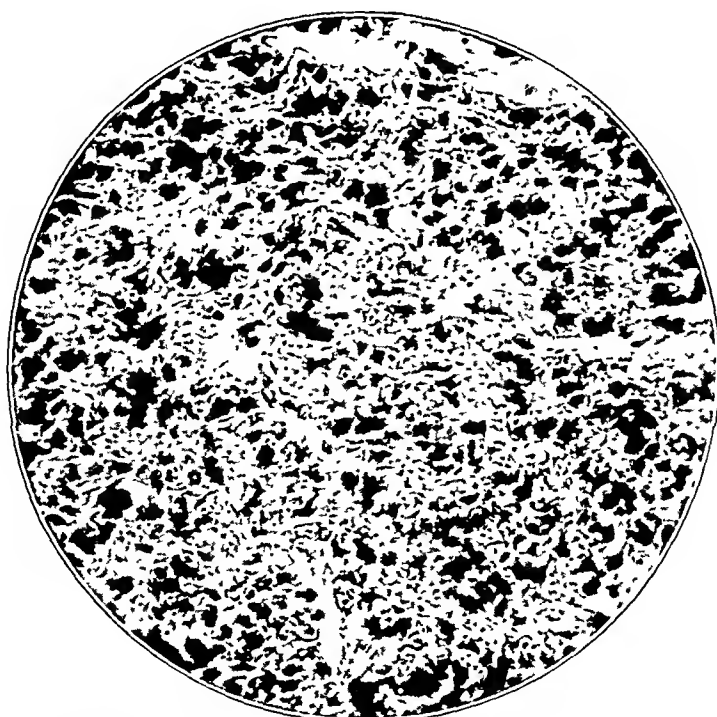


Fig. 12 (dog 610B).—Microscopic appearance of atelectatic right lung showing complete collapse of the alveoli; $\times 450$.

ever, in view of these experiments it appears probable that there are communications between the alveoli of the many lobules of a lobe of the lung. The obstructed portion of the lung is evidently retained in the inflated condition by air passing this portal of entry, which explains why collapse is not obtained when a part of the lobe is left unobstructed.

In the third group of experiments an attempt was made to eliminate all factors that might produce a forced respiratory effort. Massive atelectasis was always produced in the presence of normal respiration. That diminished respiratory excursion causes an accumulation of secretion in the air passages is still a debatable question. Many postoperative neurosurgical patients exhibit a shallow, effortless type of respiration for many hours, with seldom the production of massive atelectasis or pneumonia. Also, it is not uncommon to see massive atelectasis in patients with a respiratory excursion of normal range.

Clinical cases of obstructive pulmonary atelectasis may perhaps be divided into two groups according to the rate of production. Although as yet there has been no direct evidence of valvular obstruction producing massive atelectasis clinically, it appears likely that cases occurring within a few minutes¹³ after obstruction do so by means of a check-valve arrangement similar to that described in a former communication.¹ There is another group of patients in which the condition develops slowly, over a period of hours. This is comparable to the rate at which atelectasis was produced in the foregoing experiments, which were controlled both bronchoscopically and roentgenologically.

CONCLUSIONS

1. Complete obstruction of the air passages of an entire pulmonary lobe was essential to the production of massive atelectasis.

2. Complete obstruction of the air passages of part of a lobe was not accompanied by atelectasis of the obstructed part.

3. No particular form of respiration was essential to the production of massive collapse. (The rate of production may be increased by a valvular obstruction and a straining type of respiration.)

4. Communications appeared to be present between the alveoli of adjacent lobules of a pulmonary lobe in dogs.

5. Pulmonary suppuration was not associated with obstructive pulmonary atelectasis produced experimentally in dogs.

13. Bergamini and Sheppard: *Ann. Surg.* **86**:35, 1927. Lilienthal, in discussion on Leep, W. E.; Ravdin, I. S.; Tucker, G., and Pendergrass, E.: *Experimental Atelectasis*, *Arch. Surg.* **18**:242 (Jan.) 1929.

CALCIFICATION IN THE SUBCUTANEOUS TISSUES

REPORT OF A CASE ASSOCIATED WITH CHRONIC ATROPHIC ARTHRITIS *

HAROLD J. SHELLEY, M.D.

Assistant Attending Surgeon, St. Luke's and Knickerbocker Hospitals
NEW YORK

A brief résumé of the various theories advanced to explain the formation of the deposits of calcium or calcification follows.

Pauli and Samec¹ showed that in a colloidal albuminous solution, calcium carbonate and calcium phosphate are many times more soluble than in water. These salts could therefore be carried in the blood in nearly the same form as they are found in the deposits.

Holt, La Mer and Chown² demonstrated that blood serum is normally saturated up to 200 per cent with neutral calcium phosphate, and that this salt will remain for days without precipitating. They thought, however, that most of the calcium is carried in the form of the much more readily soluble acid carbonate and acid phosphates which may be changed into the neutral salts by the loss of carbon dioxide.

Barille³ held that calcium is contained in the blood as a double salt, calcium carbonophosphate, unstable and soluble only in the normal concentration of carbon dioxide in the blood. If the carbon dioxide is reduced locally, this unstable double salt breaks down into its two constituents which are then converted into the neutral carbonate and neutral phosphate in the proportion in which these salts are found in bone.

Wells⁴ found that this proportion by weight is 15 parts of calcium carbonate to 85 parts of calcium phosphate, i. e., in the proportion of 1 molecule of carbonate to 3 of phosphate. In pathologic calcification, he found these two salts in the same proportion.

* Submitted for publication, Dec. 5, 1930.

1. Pauli, W., and Samec, M.: Ueber Löslichkeitsbeeinflussung von Electrolyten durch Eweisskörper, *Biochem. Ztschr.* **17**:235, 1909.

2. Holt, L. E.; La Mer, V. K., and Chown, H. B.: Studies in Calcification: I, II and III, *J. Biol. Chem.* **64**:509, 1925.

3. Barille, A.: De l'action de l'acide carbonique sous pression sur les phosphates métalliques; combinaison (carbonophosphates) ou dissolution, applications diversés, *J. de pharm. et chim. (series 6)* **19**:14, 71, 196, 245 and 295, 1904; (series 7) **1**:342, 1910.

4. Wells, H. G.: Pathologic Calcification, *J. M. Research* **9**:491, 1906; *Chemical Pathology*, Philadelphia, W. B. Saunders Company, 1918.

Barille³ and Wells⁴ explained pathologic calcification because of the supposition that the blood and tissues hold their calcium salts in solution only because of a fixed content of carbon dioxide in the same solution. When the amount of carbon dioxide is decreased beyond a certain point, the salts precipitate. In places of low grade activity, the content of carbon dioxide would probably be low. Such situations would exist in areas of necrosis or fibrosis, thrombosed vessels or hematomas and the colloid in the thyroid gland.

Klotz⁵ explained calcification in certain areas of necrosis as follows: Fatty acids form in the necrotic tissues and react with soluble sodium and potassium salts in the blood and tissues to form soaps. Soluble calcium salts react with the soaps to form insoluble calcium soaps which are precipitated. By the constant exposure of the soaps to the influence of carbonate and phosphates in the body fluids, a gradual conversion of the calcium soaps into calcium carbonate and phosphate occurs.

Watt⁶ and others could find no evidence that cellular activity played a part in the formation of deposits of calcium.

REPORT OF CASE

History.—Mrs. S. C., aged 63, a widow, a housekeeper, was born in Canada and spent her entire adult life in various parts of the United States. She was referred in October, 1929, by Dr. Carl B. Davis of Chicago, because of tender nodules beneath the skin of the buttocks, the hips and the left forearm.

In 1915, she was seen by Dr. E. E. Irons of Chicago, at which time she had a maxillary sinusitis, a number of retinal hemorrhages, a high grade secondary anemia and chronic arthritis. Her blood pressure was 115 systolic and 70 diastolic; the urine was normal; the Wassermann reaction of the blood was negative. She then had treatments for the sinusitis, and several abscessed teeth were removed.

Early in 1920 she first noticed some tender lumps in the left buttock, which at times were painful. On Aug. 21, 1920, Dr. James I. Case of Battle Creek Sanitarium excised one for diagnosis.

The pathologic report by Dr. A. S. Warthin was as follows:

When cut open, the mass appeared to be more or less tubular. The interior of these tubes contained a white semiliquid material. Microscopic examination showed masses of deposits of lime salt surrounded by trabeculae of dense connective tissue. The deposits were in areas suggestive of fat lobules. They were the so-called "fat-stones," calcification following the necrosis of fat. There were also areas of old hemorrhage showing foreign body cells and phagocytes containing hemosiderin. This could probably be explained by some old traumatic injury.

The diagnosis was calcification following the necrosis of fat.

5. Klotz, O.: Studies upon Calcareous Degeneration, *J. Exper. Med.* **7**:633, 1905; On the Presence of Soaps in the Organism in Certain Pathological Conditions, *Am. J. Physiol.* **13**:21, 1905.

6. Watt, J. C.: The Deposition of Calcium Phosphates and Calcium Carbonate in Bone and in Areas of Calcification, *Arch. Surg.* **10**:983 (May) 1925; The Deposition of Calcium Salts in Areas of Calcification, *ibid.* **15**:89 (July) 1927.



Fig. 1—The subcutaneous nodules over the left iliac fossa.



Fig. 2—The nodule at the site of the blow over the left ulna.



Fig. 3.—The thoracic spine, which shows an atrophic arthritis with some destruction of the vertebral bodies.

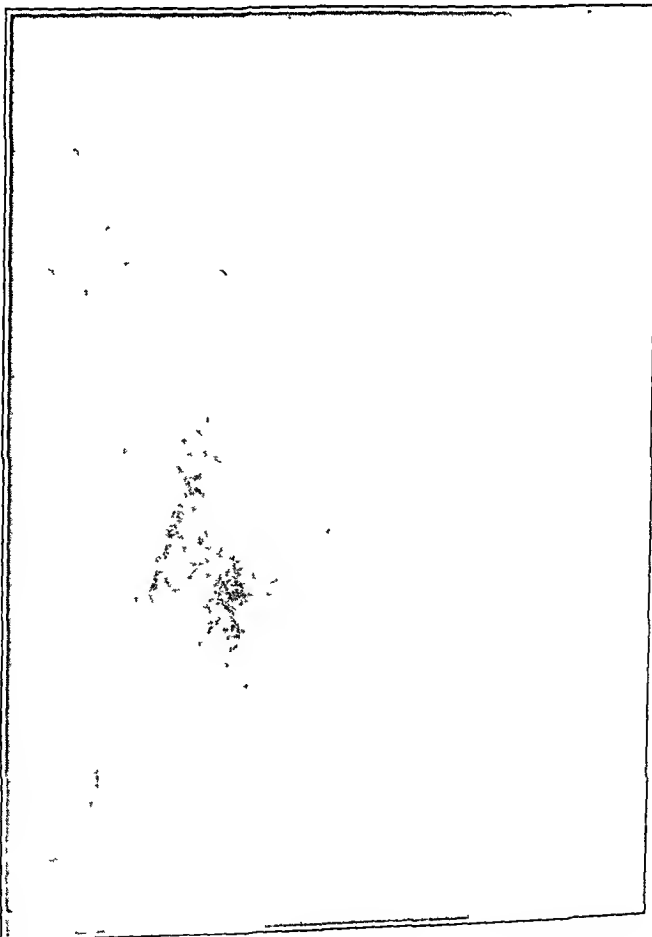


Fig. 4.—Roentgenogram of the nodules over the left iliac fossa.

During the following four years, similar tender lumps appeared over the right hip and in the right buttock in the region of the ischial tuberosity. These were excised by Dr. Carl B. Davis on May 7, 1924.

The pathologic report from the laboratory of the Presbyterian Hospital, Chicago, was as follows:

Macroscopic Examination—The tissue consisted of two masses, each containing a rather large, hard, firm nodule, about which was a cluster of smaller nodules. One large nodule was adherent to the skin. On cut section, there was a thick, whitish substance resembling white lead which oozed out.

Microscopic Examination—There were many well defined areas containing an opaque and granular substance. These were surrounded by a dense fibrous connective tissue. In a few areas the granular substance resembled crystals.



Fig. 5.—Roentgenogram, showing the two groups of nodules in the buttocks. The femoral arteries are markedly calcified.

The diagnosis was subcutaneous calcification.

The patient was admitted to St. Luke's Hospital on Oct. 24, 1929. Since her discharge from the Presbyterian Hospital, similar tender nodules had appeared over the left hip, and those on the left buttock had increased in number and size. She had struck her left forearm, and a permanent tender swelling appeared at the site of the injury. The arthritis and the severe anemia had never shown any improvement. The fourth toe on the left foot had developed into a severe grade of hammer toe.

Physical Examination—Physical examination showed an anemic, poorly nourished white woman. The skin was very dry and in areas, particularly over the cubital fossae, had the appearance of containing a white chalky deposit. Over the



Fig. 6.—Roentgenogram of the nodule over the left ulna. The arrangement of the calcification in the nodule is shown better here than in the other figures.



Fig. 7.—The pelvis and the buttocks after removal of the nodules.

left iliac fossa and posteriorly in the left buttock were small, irregular, hard, movable masses. They varied in size from that of a pea to that of a walnut. Some were adherent to the skin, and others could be moved freely beneath the skin. There was a more superficial nodule on the dorsal aspect of the left forearm. The fourth toe of the left foot showed a severe grade of hammer toe. All of the joints of the hands and feet were nodular and limited in motion.

Laboratory Examination.—The blood count showed: hemoglobin, 57; red cells, 2,900,000; white cells, 5,400; polymorphonuclear leukocytes, 52, and lymphocytes, 48. The morphology of the red blood cells was normal, except for a slight poikilocytosis. The Wassermann reaction was negative.

Chemical analysis of the blood showed: urea nitrogen, 10 mg.; sugar, 100 mg.; uric acid, 2.8 mg.; plasma chlorides, 6.5 mg., and calcium, 11.8 mg. per hundred cubic centimeters of blood. The coagulation time was two minutes.

The urine was normal, except for a few pus cells.

The basal metabolic rate was -12 per cent.

Roentgen Examination.—Films of the pelvis, taken on October 25, showed deposits of calcium in the region of the left hip about half way between the crest of the ilium and the greater trochanter. This calcified mass of bodies appeared to be in the soft tissues. There was also calcification in the soft tissues in the area of the buttocks, especially on the left.

Two inches beyond the left elbow was a cluster of calcified bodies in the soft tissues. The joints, particularly of the hands, feet and spine, showed a marked atrophic arthritis.

There was generalized calcification in the walls of the arteries. The fields of the lungs appeared clear. Examination of the nasal accessory sinuses showed them to be fairly clear throughout. There was a slight thickening in the region of the right ethmoid.

Operation.—On October 26, with the patient under general spinal anesthesia and local anesthesia in the arm, all of the palpable nodules were excised. The hammer toe was amputated. When cut, the skin gave a marked grating sensation. The nodules were found to be in the subcutaneous fat. Those over the hip were adherent to the fascia lata.

Pathologic Examination (by Dr. Leila C. Knox).—*Macroscopic Examination:* The specimen consisted of six pieces of tissue from the arm, buttock and iliac region and a hammer toe. The latter showed no lesions, except the angulation at the interphalangeal joint and a callosity of the dorsal side. The other fragments varied in size, the largest being 7 by 6 by 3 cm., with an area of normal skin. The masses were very hard and consisted of about half fat; the rest was a solid grayish tissue in which were many calcified yellowish areas.

Microscopic Examination: Sections of the tissue showed fibrous trabeculae nearly filled with amorphous and crystalline material. Most of it was calcified. There was no formation of bone and no cellular tissue. These areas were surrounded by a few fibroblasts or hyaline fibrous material from the subcutaneous fascia. Occasionally there were considerable numbers of foreign body giant cells surrounding the smaller calcified nodules.

Chemically, this substance consisted mostly of the salts of calcium with small amounts of magnesium and traces of other metallic substances.

There was no tumor or tuberculosis.

Diagnosis.—The diagnosis was calcified nodules in the subcutaneous fat of the arm and the buttocks; hammer toe.

SUMMARY

A case showing peculiar areas of calcification in the subcutaneous tissues is reported. The appearance of the skin and the grating sensation when it was cut would appear to indicate the presence of a fine deposit of calcium in the skin also.

Although the majority of the deposits showed a bilateral symmetry, their locations were such that trauma could be the etiologic factor in producing conditions that favor calcification. The deposit on the forearm followed a definite and severe blow in the exact location. The buttocks over the ischial tuberosities and the areas above the greater trochanters receive constant trauma, particularly in a very thin person, as was the patient in the case reported.

It is of interest that this condition should be found in a patient with a marked atrophic type of chronic arthritis. The density of the bones is much decreased, even though the skin and subcutaneous tissues contain deposits of calcium. The chemical composition of the blood and the basal metabolism do not appear to have any relation to the local condition, unless the low basal metabolic rate and anemia give a low carbon dioxide content in the tissues. Conditions favorable to a deposit of calcium salts would then be much more readily created.

The severe grade of anemia is probably a part of the long-standing arthritis.

1148 Fifth Avenue.

FORTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY *

PHILIP D. WILSON. M.D.

LLOYD T. BROWN, M.D.

M. N. SMITH-PETERSEN, M.D.

JOHN G. KUHN. M.D.

AND

EDWIN F. CAVE, M.D.

BOSTON

RALPH K. GHORMLEY. M.D.

ROCHESTER, MINN.

MURRAY S. DANFORTH, M.D.

PROVIDENCE, R. I.

GEORGE PERKINS

LONDON, ENGLAND

ARTHUR VAN DESSEL. M.D.

ANTWERP, BELGIUM

AND

C. HERMANN BUCHOLZ, M.D.

HALLE, GERMANY

CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—Evans¹ reexamined twenty-five of seventy patients with congenital dislocation of the hip whom he had treated between 1903 and 1920. He found one bad, two poor, thirteen good and nine perfect results, using function as a criterion. Roentgen examination showed that of the thirty-two hips reduced, there were three anterior transpositions, five eccentric nearthroses, sixteen concentric reductions and eight normal hips. The treatment in these cases was closed reduction, followed by prolonged fixation in one position (90 degrees of flexion, 70 degrees of abduction, 0 degrees of rotation) for a period varying from one to eighteen months. Evans allowed walking at once with a 6-inch (15.24 cm.) patten, but after removal of the plaster, the child was kept recumbent for three months and allowed

* This Report of Progress is based on a review of 163 articles selected from 393 titles dealing with orthopedic surgery appearing in the medical literature between Jan. 1, 1931, and April 4, 1931, supplemented by a few articles of older date. Only those papers that seem to represent progress have been selected for review.

1. Evans, E. L.: Brit. M. J. 2:1035 (Dec. 20) 1930.

to kick about in bed by day and held splinted in the old position by night. For three months after walking had recommenced, a patten of 1½ inches (3.77 cm.) was worn on the sound side to hold the affected leg abducted.

Kidner² stated that the tightly stretched and thickened capsule was the chief obstruction in reducing congenital dislocation of the hip in children under 10. He advised in such cases incising the capsule in a longitudinal plane, freeing particularly the adhesion of the capsule from the side of the ilium, in this way exposing the true acetabulum. After this was done he found that reduction of the dislocation was relatively easy, and that the position was maintained without great difficulty.

GROWTH DISTURBANCES OF BONE

Köhler's Disease.—Sauer³ found Köhler's disease of frequent occurrence without symptoms. The condition was often found in roentgenograms of the feet, which were taken for other diseases. He believed that it was produced by the presence of more than one center of ossification in the scaphoid bone. One case was followed in which there were two centers of ossification which later developed into typical Köhler's disease.

[ED. NOTE.—The evidence produced is not sufficient to convince us that multiple centers of ossification in the scaphoid bone are the necessary cause of Köhler's disease.]

Infantile Patella.—Mau⁴ described changes in roentgenograms of the patellae of children, which resembled the growth disturbances seen in many other epiphyses. In severe cases there was an apparent partial necrosis of the patella. The subjective symptoms were very mild. Prognosis was excellent in most cases. The author believed that the condition was an aseptic necrosis due to abnormal strain or pressure.

RICKETS AND DISTURBANCES OF CALCIUM METABOLISM

Rickets.—Holmes⁵ voiced the opinion that vitamin D and viosterol were not identical substances. He reviewed the clinical and laboratory studies on the antirachitic properties of vitamin D found in cod liver oil and compared it with that of viosterol. The data that he gathered suggested that in the treatment for rickets either vitamin D as it occurred in cod liver oil possessed properties not present in viosterol, or that vitamin A or some other substance in cod liver oil enhanced the antirachitic vita-

2. Kidner, F. C.: *J. Bone & Joint Surg.* **13**:104, 1931.

3. Sauer, W.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **40**:679, 1929.

4. Mau, C.: *Deutsche Ztschr. f. Chir.* **288**:1, 1930.

5. Holmes, A. D.: *New England J. Med.* **204**:211, 1931.

min so that it became more effective in the treatment for rickets than equivalent units of viosterol.

Compere⁶ studied the roentgen changes and the chemical reactions in the blood in ten rachitic infants and one nonrachitic patient and found that administration of cod liver oil with phosphorus was more effective in healing rickets than was administration of cod liver oil alone. When such patients were placed in ideal antirachitic surroundings and also given cod liver oil in doses of 3 to 6 teaspoonfuls daily with phosphorus, the calcium and phosphorus in the blood increased rapidly, and the healing process in the bone as shown by a roentgenogram progressed very rapidly. Phosphorus when given alone had little effect on the calcium and phosphorus content of the blood unless there had been previous stimulation by ultraviolet irradiation or the administration of cod liver oil.

Bunker and Harris⁷ studied the antirachitic protective action of various portions of the light spectrum. Rats were given the Steenbock rachitic diet, and were exposed to mercury vapor lamps of standardized voltage and distance. They found that the light given by the lamp gave uniform protection, but that if it was followed by exposure to the infra-red portion of the spectrum alone, only one third of the animals were protected. If the infra-red exposure preceded the exposure to the entire spectrum from the lamp, two thirds of the animals were protected against rickets. Exposure to infra-red alone gave no protection. Where all light below 3,000 angstrom units was filtered out and infra-red was present, 23 per cent of the animals were protected. If all light below 3,000 angstrom units plus the infra-red was filtered out, 43 per cent of the rats were protected.

Calcium in the Healing of Fractures.—Speed⁸ concluded from his studies on dogs and in a series of consecutive cases in human beings that the diminution of the calcium-phosphorus ratio in the blood had little or nothing to do with the rate of healing of fractures, and that such determinations offered little in helping determine a prognosis as to the speed of union.

Osteitis Fibrosa.—Hunter⁹ reported a case of osteitis fibrosa in a 37 year old woman, who was treated by parathyroidectomy. There was marked improvement following the operation with increase in weight, disappearance of pain and restoration of menstruation. The bony

6. Compere, E. L.: Effect of Phosphorus on Rickets: Roentgenologic Changes in Rickets Following Administration of Phosphorus, *Am. J. Dis. Child.* **40**:1177 (Nov.) 1930.

7. Bunker, J. W. M., and Harris, R. S.: *Am. J. Pub. Health* **20**:1287, 1930.

8. Speed, K.: *J. Bone & Joint Surg.* **13**:58, 1931.

9. Hunter, D.: *Proc. Roy. Soc. Med. (Clin. Sect.)* **24**:40, 1930-1931.

tumors (osteoclastomas) gradually disappeared, although by roentgen examination the bone density remained the same. Tetany followed operation and lasted seventeen days. Parathyroid extract-Collip was given from the sixth to the twenty-sixth day. The serum calcium, which before operation was about 12 mg. per hundred cubic centimeters, dropped to about 9 mg.; the plasma phosphorus was unchanged. The excretion of calcium, although considerably lower after operation, still remained higher than the intake of calcium five months after the operation. The histologic appearance of the parathyroid suggested hyperplasia and exceptional functional activity rather than an autonomous neoplasm. The bone tumors could not be differentiated from the giant cell tumors occurring at the ends of long bones in skeletons free from general change.

Parathyroid Disturbances.—Quick and Hunsberger¹⁰ reported a case of hyperparathyroidism in a man of 21 who became helplessly deformed in three years. The first symptoms were polydipsia, polyuria, a persistently milky urine and sharp myositic and arthritic pains. The roentgenograms showed decalcification of the bones and considerable calcification of the peripheral arteries. A persistent hypercalcemia was found. A parathyroid tumor was found and removed with considerable difficulty. General improvement followed the removal of the tumor. The authors advised the use of vitamin D or viosterol to minimize parathyroid tetany and to hasten the recalcification after the removal of a parathyroid tumor.

Parathyroid Extract.—In an editorial¹¹ in *The Journal of the American Medical Association* the influence of parathyroid extract on bone salts was discussed. A hypofunction of the parathyroid gland appeared to exert an inhibiting effect on the rate of healing of fractures while administration of the glandular hormone seemed to favor calcification and union of fractures. When parathyroid extract was injected, a marked increase in the blood calcium resulted. Experiments by Tsai and Hsu afforded evidence that the origin of the increased calcium concentration was from the bones. The difficulty of raising the blood calcium level by giving large doses of viosterol to parathyroidectomized animals and the failure to raise the concentration of calcium in the blood of animals deprived of vitamin D were additional suggestive observations that the calcium came from the bones through the stimulus of parathyroid extract. As studies of the calcium balance in lactation also showed, the bones were a readily available reservoir of mineral salts. Extraction and deposition of calcium in relation to the bones were

10. Quick, A. J., and Hunsberger, A., Jr.: Hyperparathyroidism: Clinical Picture in Far Advanced Stage, *J. A. M. A.* **96**:745 (March 7) 1931.

11. Influence of Parathyroid Extract on Bone Salts, *Editorial*, *J. A. M. A.* **96**: 443 (Feb. 7) 1931.

probably being carried on constantly in the body after the removal of a parathyroid tumor.

TUBERCULOSIS

Future Research.—Long,¹² in discussing the recent advances in research on tuberculosis, mentioned the finding of nonacid-fast forms of the tubercle bacillus which were highly pathogenic, but which were rarely found in cold abscesses. Pleomorphic forms and even filtrable viruses produced the pathologic picture of tuberculosis in animals. Another advance was the division of tubercle bacilli into rough and smooth forms, the smooth form being of high pathogenicity and growing best in alkaline mediums and the rough form of low virulence and growing best in acid mediums. The rapid changes in form and virulence in the same strain of the bacillus tuberculosis, the author considered a potent argument against vaccination for tuberculosis. Opinions in tuberculosis of any type should be based on disturbed function rather than on altered structure and should never be based on roentgenograms alone. In the treatment for the disease no specific drug had been found of definite value. The increased application of heliotherapy was the best measure in nonpulmonary tuberculosis. A high monocyte count was of unfavorable significance. The future work should be on prevention of transmission rather than on vaccination which was still *sub judice*.

Treatment.—Gaugele¹³ advocated the use of careful, active, assisted motion in tuberculous joints after the acute stage was past in preference to the older method of immobilization for a long period of time with the hope that bony ankylosis would result. The patients treated this way were either kept in traction or used nonweight-bearing splints (Hessing type) for a long period. Early results were good, but no case is of long enough duration for final judgment to be passed.

SPINAL LESIONS AND BACK PAIN

Intervertebral Disk.—Schmorl¹⁴ pointed out that calcification of the nucleus pulposus of the intervertebral disk was a rather rare occurrence. Very rarely the whole disk was calcified. The calcification of the nucleus was a sign of degeneration. Calcification and ossification were not the same. In infectious spondylitis the intervertebral disks were rarely affected.

Lyon¹⁵ disagreed with the opinion of Schmorl that the intervertebral disks were but rarely affected in infectious spondylitis on the basis of the literature and x-ray pictures. In typhoid spondylitis the intervertebral disk was often calcified in the healing process.

12. Long, E. R.: Colorado Med. 28:5, 1931.

13. Gaugele, C.: Chirurg. 2:163, 1930.

14. Schmorl, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen 40:18, 1929.

15. Lyon, E.: Fortschr. a. d. Geb. d. Röntgenstrahlen 40:635, 1929.

Schmorl¹⁶ described small enchondromas on the posterior aspect of the intervertebral disks. He believed that they originated through the tearing off of the edge of the intervertebral disk; the soft tissue of the nucleus pulposus was then forced out beneath the posterior longitudinal ligament and cartilage proliferation followed. Where the enchondroma was somewhat calcified, it could be demonstrated in the roentgenograms.

[ED. NOTE.—Schmorl's studies of spinal pathology have been far-reaching and his contributions on lesions of the nucleus pulposus deserve careful study.]

Low Back Pain.—Miltner and Lowendorf¹⁷ reviewed the records of 2,050 cases of low back pain at the University of Iowa Hospital, and found the causative factors to be as follows: (1) osteo-arthritis, 1,350 cases; (2) sacro-iliac and sacrolumbar strain, 525 cases; (3) muscle strain, 100 cases; (4) lumbar myositis, 25 cases, and (5) rarer lesions, such as fractures of the transverse process, spondylolisthesis, etc., 50 cases.

They emphasized the importance of a careful history and an accurate physical examination, making use of the special tests in a differential diagnosis. The roentgenogram was relied on relatively little except as a means of ruling out gross deformity or disease. The chief means of treatment consisted of (1) rest in the acute cases followed by (2) physical therapy and exercises supplemented by support in the form of (3) brace or belt, (4) manipulation, and (5) operative treatment, which was resorted to only in the resistant cases.

Spondylolisthesis.—According to Meyerding,¹⁸ prior to 1900 only 125 cases of spondylolisthesis had been recorded in the literature, and all but 6 of these had been reported by obstetricians or gynecologists. With the perfection of roentgen technic, however, the diagnosis became easy. From 1918 to 1930, 121 cases were observed at the Mayo Clinic. Sixty-two per cent were in males, and the average age was 37 years. Thirty-eight per cent ascribed the deformity to trauma. The symptoms were low backache, pain in the legs, and at times numbness and tingling. Rest usually gave relief, as did a plaster jacket or brace. Fusion of the lumbosacral spine, however, offered the most permanent form of relief.

Four cases of spondylolisthesis were reported by Kleinberg,¹⁹ in which the conditions seemed to be due to a congenital deformity of the posterior arch of the fifth lumbar vertebra. In two of these cases there was a cleft in the pedicles with a wide separation of the superior and

16. Schmorl, G.: Fortschr. a. d. Geb. d. Röntgenstrahlen 40:629, 1929.

17. Miltner, L. J., and Lowendorf, C. S.: J. Bone & Joint Surg. 13:16, 1931.

18. Meyerding, H. W.: J. Bone & Joint Surg. 13:39, 1931.

19. Kleinberg, S.: Am. J. Surg. 10:521, 1930.

inferior articular processes. In the other two the laminae were attenuated and abnormally long. In all of these cases trauma was an important factor in bringing on symptoms. The author believed that a fusion operation was imperative where there was a cleft in the pedicles. In the type with abnormally long laminae some external spinal support should first be tried for the relief from pain.

POLIOMYELITIS

Immunization.—A recent editorial²⁰ in *The Journal of the American Medical Association* gave a summary of the knowledge on immunology in poliomyelitis. Most investigators were convinced that poliomyelitis was caused by one of that still vague category of agents, the filtrable viruses. Flexner and Lewis and Levaditi and Landsteiner discovered in 1910 that the serum of patients convalescent from poliomyelitis was capable of neutralizing the filtrable virus. According to Park, the serum from slight abortive cases was on the average as potent as that from pronounced cases. The serum of many persons who have never had poliomyelitis contained antibodies, but these were not so potent as in the serum of convalescent cases. The antibodies remained for a long time in the blood of persons who were convalescent. Rhoads recently discovered that poliomyelitis virus could be inactivated by suspensions in aluminum hydroxide. This reaction was promoted by an acid medium and could be prevented by an alkaline environment. The striking feature, however, was the demonstration that the virus, when absorbed in aluminum hydroxide, was incapable of producing poliomyelitis but was still capable of inducing active immunity in monkeys (*Macacus rhesus*). In a small series of animals thus immunized symptoms of experimental poliomyelitis did not appear, and in only one was the degree of immunity, although adequate to protect against nasal injection, sufficient to protect against intracerebral injection of virus. Intracerebral inoculations of the aluminum suspension alone were without pathologic effect. The mere recital of these experiments offers a bright prospect of helpful possibilities in the attack on infantile paralysis. It has depended and will continue to depend on animal experimentation.

Stewart and Platou²¹ stated that the use of convalescent serum was of definite value in the preparalytic stage of poliomyelitis. They advised the use of from 20 to 30 cc. intrathecally and 50 cc. intravenously. They advised a wider use of prophylactic doses of from 10 to 20 cc. of convalescent serum subcutaneously to exposed children during an epidemic.

20. Immunization Studies in Poliomyelitis, Editorial, J. A. M. A. 96:119 (Jan. 10) 1931.

21. Stewart, C. A., and Platou, E. S.: Minnesota Med. 14:42, 1931.

Neustaedter²² reviewed the work of Flexner in which immune bodies against poliomyelitis could not be obtained after the injection of filtrable virus into the horse. In 1916, the author injected into a horse trypticized filtrates of cord and brain suspensions of children that died of poliomyelitis. The serum of this horse protected one monkey completely from an intracerebral inoculation of 0.5 cc. of a 5 per cent suspension of a very potent virus. Since that time three more horses have been inoculated with equally good results. It was found possible to concentrate this serum sufficiently to neutralize 100 parts of poliomyelitis virus in vitro. The author stated that the efficacy of this serum, and that of Pettit of Paris who followed his method, had been shown in over sixty frankly paralytic cases of poliomyelitis.

Diagnosis.—Allaria²³ gave a résumé of the present knowledge determining the diagnosis of acute anterior poliomyelitis, paying especial attention to the importance of abortive cases and of so-called carriers. He stressed the importance of quarantine and urged that it be carried out for a month, or better, for a month and a half. The author stated that the use of serum from patients who have recovered was of value if given early, as was probably also the serum from horses immunized by the method of Pettit.

[ED. NOTE.—Evidence is steadily accumulating that tends to show the value of serums in the preparalytic stage of poliomyelitis. Unfortunately, it is in this stage that diagnosis is peculiarly difficult. The development of mass immunization or a rational form of temporary immunization during epidemics is suggested by these papers as a possible method of bringing the disease under control.]

PYOGENIC INFECTIONS

Osteomyelitis of the Spine.—Carson²⁴ recorded four cases of sub-acute osteomyelitis of the spine, three in adults and one in a child. All recovered. In three of the four the illness began with a boil on the skin. The genito-urinary tract was also involved in every case. Staphylococcus aureus was cultivated from all four patients. Three developed an abscess in connection with the spine. Attention was directed to the spine by severe nerve root pain.

Epiphysitis.—Miller²⁵ studied seventy-seven cases of acute transient epiphysitis of the hip. The average age of the patients was 7½ years.

22. Neustaedter, M.: Antipoliomyelitis Horse Serum, J. A. M. A. 96:933 (March 21) 1931.

23. Allaria, G. B.: Riforma med. 41:1779 (Nov. 10) 1930.

24. Carson, H. W.: Brit. J. Surg. 18:400, 1931.

25. Miller, O. L.: Acute Transient Epiphysitis of Hip Joint, J. A. M. A. 96:575 (Feb. 21) 1931.

The average duration of the symptoms before admission to the hospital was seven weeks. The average temperature on admission was slightly more than 100 F., and elevation of temperature was noticed for five weeks. The average leukocyte count on admission was 15,000 with 81 per cent polymorphonuclear cells. The average time of duration of symptoms, local or general, after admission to the hospital, was six weeks. Miller found this condition a common cause of hip complaint in children. It was usually provoked by mild trauma. It was suspected in a child who complained of pain about the hip if he had diseased tonsils or had recently had an acute infectious disease. Eighty per cent of the cases were associated with diseased tonsils. Carefully made roentgenograms suggested small abscess formation and absorption about the epiphyseal line. The treatment consisted of removal of infectious foci, rest from weight-bearing and traction of the involved limb. The duration of the disease was from a few weeks to a few months, and if prompt treatment was instituted, the children recovered without any permanent changes in the hip joint.

[ED. NOTE.—Some of the authors have observed a number of similar cases. In the majority of these, symptoms in the hip or knee followed a gastro-intestinal disturbance. With rest and regulation of the enteric tract, complete recovery ensued. Roentgenograms showed no changes. These cases were commonly diagnosed as toxic arthritis. If demonstrable changes can be observed at the epiphyseal line, the name acute, transient epiphysitis is a far more logical one for these cases.]

CHRONIC ARTHRITIS

Problem of Arthritis.—In an address before the New England Health Institute, Osgood²⁶ quoted statistics to indicate that arthritis was the most prevalent of the chronic ailments. He emphasized the fact that arthritis was a generalized disease with joint manifestations and that there were certain types of persons in whom there was a predisposition to the disease. He outlined the outstanding characteristics of the two great types, i. e., atrophic and hypertrophic arthritis. While local treatment of the joint was important, he stated that general treatment of the patient, especially early in the disease, was of the utmost importance.

In speaking of the developments in the problem of arthritis, Pemberton²⁷ said that in the opinion of most of the members of the American Committee for the Control of Rheumatism it was of the first importance to envisage arthritis as a whole instead of focusing on any

26. Osgood, R. B.: New England J. Med. **204**:55, 1931.

27. Pemberton, R.: Developments in Problems of Arthritis, J. A. M. A. **96**:33 (Jan. 3) 1931.

factor, be it mechanical, bacteriologic or nutritional, which may precipitate it. As in tuberculosis, the specific treatment was based on broad physiologic considerations, since the organism was of necessity practically ignored in a therapeutic sense, so in arthritis the treatment should be on broad physiologic grounds. No agency or organism was recognized by the committee as the single cause.

Treatment of Arthritis of the Spine.—Jepson and Brav²⁸ reported four cases of arthritis of the spine in which the patients were treated by manipulation to correct the forward flexion of the spine. Under ether anesthesia, the portion of the spine showing the greatest deformity was manipulated. Following manipulation a plaster cast as applied in hyperextension. This was followed by a brace. The authors felt that this method was of value where no bony ankylosis was shown by the roentgenogram.

[ED. NOTE.—While deformity in the spine may be corrected to a certain extent by this method, several of the authors have observed catastrophes following its use. Gradual hyperextension with sandbags or posterior shells will accomplish as much without injury, and in as short a time, considering the after treatment. In a number of cases ankylosis of the spine cannot be determined on roentgen evidence alone.]

NERVOUS DISORDERS

Tabetic Arthropathy.—In discussing the tabetic arthropathies, Steindler²⁹ stated that while it must be expected that the neurogenic background predisposed the joint to arthropathic disintegration, it seemed certain that mechanical and traumatic events were the determining factors that sooner or later led to the breakdown of the articulation. Protection against these influences by early and adequate splinting. preservation of protecting musculature by physical therapy and, above all, early stabilization and alinement by conservative or operative means furnished the best prospects of extending the usefulness of these joints for many years. Steindler advised detection of the arthropathic joint by roentgen examination in the preataxic stage, and then immediate and adequate protection of the joint to prevent the action of detrimental external influences.

From his own observations, Iselin³⁰ came to the conclusion that in cases of so-called tabetic arthropathia the tabes was not the only underlying cause, but that in many cases the disease was caused by a combination of syphilis, other infections, nutritive disturbances and nervous

28. Jepson, P. N., and Brav, E. A.: *Am. J. Surg.* **10**:285, 1930.

29. Steindler, A.: *The Tabetic Arthropathies*, *J. A. M. A.* **96**:250 (Jan. 24) 1931.

30. Iselin, H.: *Deutsche Ztschr. f. Chir.* **227**:414, 1930.

damages of tabetic origin. Of these syphilis seemed to be most important. The syphilis could be reactivated by traumatism or without any special cause within the arthropathic joint.

[ED. NOTE.—We think that Steindler has voiced the consensus of orthopedic opinion in regard to the etiology of tabetic arthropathy.]

Ramisection in Spastic Paralysis.—Carrell³¹ studied the end-results in eighty-three sympathetic ramisections; twenty-three cervical and sixty lumbar. There were no differences in the character of the reflexes before or after the operations. The record of footprints did not give any particular information. No change was observed in fixed contractions or in those contractions that developed on attempting motion or excitation, as scissor gait, equinus or valgus of the foot. Relief of contractions by other operations had been necessary, but it was noted that a paraplegia of equal spasticity had better function in the leg with lumbar ramisection and section of the obturator than with obturator section alone. Carrell concluded that the severity of physical disability and mental development were the two important factors influencing the progress after such operation. Where it was necessary to choose between ramisection and Stoffel's operation with foot stabilization, the latter procedure seemed to meet more indications, and they gave a higher percentage of improvement in a large series of cases.

Compression of the Cord by Bony Plaques.—Four cases of compression of the spinal cord by bony plaques in the meninges were reported by Punsepp.³² Osseous deposits in the arachnoid, while frequently observed, gave no symptoms. Trauma probably played a rôle in these cases. These bony plaques were characterized by an abundant formation of connective tissue in which the osseous deposits occurred. In these four cases laminectomy was performed after neurologic symptoms, and block with iodized poppy seed oil 40 per cent showed the area involved. One patient died of cardiac failure. There was complete recovery in the other three.

NEOPLASMS

Osteitis Fibrosa Localisata.—Ferber³³ studied the localized form of osteitis fibrosa in adults. He found this form most frequent in young adults in the form of a solitary cyst of the bone. Adults in middle or old age were affected much less frequently. In these cases the formation of an actual cyst was not as typical as the formation of fibrous marrow, osteoid and bony new growth. Prognosis was comparatively favorable. The disease might last for many years without much change

31. Carrell, W. B.: Sympathetic Ramisection in Spastic Paralysis, J. A. M. A. 96:849 (March 14) 1931.

32. Punsepp, L.: J. Nerv. & Ment. Dis. 73:1, 1931.

33. Ferber, H.: Ztschr. f. orthop. Chir. 53:285, 1930.

or disturbance of function. Consequently, the therapy should usually be conservative. Operative treatment was indicated to correct deformity or to improve the appearance by removal of hypertrophic bone. Differentiation from Paget's disease consisted in that the latter had a marked progressive tendency, whereas osteitis fibrosa, especially in the localized form, usually came to a standstill, and did not spread to other parts of the skeleton.

[ED. NOTE.—Pathologic fracture is a frequent complication of localized osteitis fibrosa. We have observed cysts that have persisted in spite of two or three fractures, and we think that operative treatment is indicated under such conditions.]

MISCELLANEOUS

Malacia of the Semilunar and Scaphoid Bones of the Wrist.—Santozki and Kopelmann³⁴ made a study of nineteen cases of malacia of the semilunar and scaphoid bones of the wrist. They considered the process to be an aseptic necrosis of the bones, and that the cause was an obliteration of the nutritive vessels brought about by chronic occupational traumatism. Individual predisposition played a part. In the opinion of the authors early excision was the best treatment.

Blaine³⁵ considered that the essential change was a softening of the bones with necrosis and deformity. He thought that a twist of or a blow on the wrist was of common occurrence, and merely resulted in the roentgen disclosure of a preexisting pathologic condition in the semilunar or scaphoid bones. Discussing the etiology, the author mentioned the various theories such as embolic obstruction to the arterial supply and the relatively poor normal blood supply to these bones, and said that since the factors of etiology, symptomatology and pathology were more or less identical with similar lesions that have been found to involve various other osseous structures of the body, it seemed logical to consider the process essentially the same, namely, osteomalacia. He felt that surgical removal of the diseased bone did not materially reduce the disability.

On the other hand, Schnek,³⁶ from his studies of the so-called post-traumatic cysts of the scaphoid bone (another name for the same process in the opinion of the editors), came to the conclusion that these cysts were the sequelae of unrecognized and improperly treated fractures of the scaphoid bone. His own experience convinced him that there was a great difference between this condition and actual pseudarthrosis of the

34. Santozki, M., and Kopelmann, S.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **39**:1060, 1929.

35. Blaine, E. S.: *Lunate Osteomalacia*, *J. A. M. A.* **96**:492 (Feb. 14) 1931.

36. Schnek, F.: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **39**:1016, 1929.

scaphoid in that the cystic condition and likewise the fresh fracture could always be cured by complete and prolonged immobilization, while the pseudarthrosis did not respond to this method of treatment.

[ED. NOTE.—We believe that the opinions of Santozki and Kopelmann and of Blaine in respect to the etiology of malacia of the scaphoid and semilunar bones or Kienboch's disease will obtain greater acceptance than Schnek's. We believe, however, that trauma, either occupational or single, is a factor. We agree with Schnek that prolonged fixation of the wrist will often bring about a cure, and that excision is rarely necessary.]

Semilunar Cartilages of the Knee.—Israelski³⁷ reported three instances of calcification of the menisci revealed by roentgen examination. All occurred in patients past middle life, and did not follow trauma. The author thought that a metabolic factor might be the cause since one patient had gout and another diabetes. In one there was also calcification of one of the intervertebral disks.

Mandl³⁸ observed regeneration of previously excised semilunar cartilages in two patients; one was found accidentally at autopsy, and the other at a later operation on the same knee joint. He was surprised to find an almost complete regeneration of the cartilage in both cases.

Changes in the Hip Joint in Hemophilia.—Loehr³⁹ examined and studied patients whose hip joints had been affected by hemophilia. The bleeding might be intra-articular or extra-articular, or even within the bony tissue. It might occur once or repeatedly, usually in early age, but sometimes even after the age of puberty. The hip joint was relatively rarely affected compared with the elbow and knee joints. Both of Loehr's patients were of preadolescent age, and showed typical signs of osteochondritis deformans juvenalis. The study of the cases reported in the literature showed that all patients who had hemophilia affecting the hip joint who had been affected before puberty showed the same condition, while patients who had been affected at a later age showed changes of a different nature, such as coxa valga, cystlike development in the neck of the femur, in the head and in the acetabulum with more or less evidence of arthritis deformans.

BONE, JOINT AND TENDON SURGERY

Physiologic Reconstruction of the Thumb after Total Loss.—The operative procedure for the reconstruction of a functioning thumb from a second metacarpal and the proximal half of the first phalanx attached

37. Israelski, M.: Am. J. Roentgenol. **25**:85, 1931.

38. Mandl, F.: Zentralbl. f. Chir. **52**:1929, 1930.

39. Loehr, D.: Ztschr. f. Chir. **228**:234, 1930.

to it was reported by Bunnell.⁴⁰ The transplantation was done so as to preserve nerve, blood and lymph supply. The second metacarpal was transplanted to the trapezium, and the lower 3 inches (7.6 cm.) of the tendon of the flexor carpi radialis was passed through drill holes in the metacarpal and trapezium to insure a stable joint. The cut tendon was then attached to the flexor carpi radialis brevis. The three extensor tendons of the thumb were attached to the second metacarpal at their usual locations. The flexor tendons of the thumb were attached to the flexor tendons of the transplanted index finger. The thenar muscles were reattached to the transplanted second metacarpal. An excellent functional result was obtained. The author gave as requisites of a transplanted thumb: sensation, motion particularly in opposition to fingers, strength and durability.

Complete Rupture of the Supraspinatus Tendon.—Wilson⁴¹ stated that an experience with ten patients with complete rupture of the supraspinatus tendon in a period of eighteen months had impressed him with the frequent occurrence of this injury. The pathologic observations at operations indicated gradual weakening of the tendon previous to rupture. The lesion should be suspected in any patient who gave a history of shoulder disability of sudden onset and particularly when a painful snap has occurred during a movement of abduction or when there had been a fall on the shoulder with or without dislocation. The characteristic sign of rupture was inability to abduct actively while this movement might be executed passively. This sign might be masked by muscle spasm or adhesions. Repair of the tendon was rendered difficult by the extent of the gap in the capsule, and it was important not only to suture the tendon to the greater tuberosity, but to provide means whereby it might develop a real bony attachment throughout its breadth. The results of operation showed that the disability could be removed and emphasized the importance of recognizing this lesion which was frequently overlooked.

Operative Treatment of Scoliosis.—In three patients with severe scoliosis with marked listing to the side, Schede⁴² used a massive graft from the tibia to hold the trunk upright. The graft was inserted between the transverse process of the first lumbar vertebra and the rim of the pelvis. The end-results were as follows: In one patient the graft was absorbed, but in the other two the graft hypertrophied to about three times its original width and gave excellent support to the trunk. While in all cases the graft became firmly united to the trans-

40. Bunnell, S.: Surg., Gynec. & Obst. 52:245, 1931.

41. Wilson, P. D.: Complete Rupture of the Supraspinatus Tendon, J. A. M. A. 96:433 (Feb. 7) 1931.

42. Schede, F.: Zentralbl. f. Chir. 57:2658, 1930.

verse process of the first lumbar vertebra, it developed an articular union to the rim of the pelvis in the form of a saddle joint.

Preoperative Determination of the Best Functional Position for Ankylosis of the Hip.—Adams,⁴³ from a study of ankylosed hips, concluded that a definite position could be determined in each case which would give the best functional result. When ankylosis of the hip was produced by operation, the hip could be fixed in this ideal position. The best functional position was determined by studying Kingsley's table for normal flexion and Lovett's table for abduction and apparent shortening.

[ED. NOTE.—There has been a wide variance of opinion as to the best functional position for ankylosis of the hip, and the tendency has been to assume that the position should be the same for all persons, an attitude that is manifestly wrong because it does not take into consideration such factors as shortening, etc. Adams has done a careful piece of work, and his article should be studied, and the rules laid down for determining the optimum position of the hip followed.]

Correction of Deformed Feet.—Basing his practice on careful study of bone regeneration and on animal experiments, Matti⁴⁴ developed a technic for correction of foot deformities and for foot stabilization in which he saved the bone obtained from the wedge-shaped excisions about the joints, cut it up into many small fragments, and transplanted the bone chips in between the denuded bone surfaces in such a position as to help maintain the corrected position. For example, in the correction of club feet he put them in on the medial side. He pointed out that bone survived the earlier and more completely it got in touch with the circulation of blood and lymph. Hence a large piece of compact bone was at a greater disadvantage than a small piece of spongy bone. His experiments on animals showed that chips of cancellous bone remained living for a long time, and served well in filling bony defects. He used the same principle in the operative correction of deformities of long bones and in the treatment for pseudarthrosis.

Rey⁴⁵ recommended the resection of the medial plantar nerve as a reliable and simple method for the cure of claw foot. The method had the advantage of attacking those muscles that were concerned with the production of the deformity and by the action of which recurrence was brought about. In patients with severe deformities, the lateral nerve

43. Adams, A. O.: Surg., Gynec. & Obst. **52**:261, 1931.

44. Matti: Zentralbl. f. Chir. **57**:796, 1930.

45. Rey, J.: Ztschr. f. orthop. Chir. **53**:322, 1930.

might be resected also and in addition the long peroneal tendon was transplanted into the short peroneal tendon, and the division of the plantar fascia was performed. In cases in which the tarsus showed severe deformation, bony resections should be done beforehand, later followed by the resection of the nerves. The following muscles were of the greatest importance in the development and in the later recurrence of pes cavus: the short flexor muscles of the toes, the long peroneal muscle, and often the abductor hallucis. Of lesser importance were the long flexor and the posterior tibial muscles, and still less the triceps surae.

Whitman⁴⁶ described an operation for the correction of equino valgus deformity resulting from paralysis of the tibialis anticus or posticus muscles, or both. It consisted in subastragalar and astragaloscaphoid arthrodesis through a mesial incision. Then the anterior tibial tendon was divided at its junction with the muscular fibers, dissected free from its sheath and passed under and then over the tendons of the extensor communis digitorum and extensor hallucis longus, and finally buried subperiosteally in the tibia.

The operation had been done eight times in seven patients. The author stated that all patients were satisfied with their results.

[ED. NOTE.—It is of interest to note that here are described three methods involving the use of three different principles for the operative correction of foot deformities: wedge-shaped excision and arthrodesis of joints, resection of the nerves supplying overacting muscles and the use of tendon loops to restrain and improve the lines of muscle pull. With the first principle, all of us are in accord. Remodeling of the bony architecture with arthrodesis of the unstable joints is the foundation stone on which everything else is built. Readjustment of muscle pulls, we believe, can be more satisfactorily brought about by tendon transplantation than by the use of a tendon loop. With the resection of the nerves to the overacting muscles in pes cavus we have had no experience, but the method may well have a use.]

FRACTURES

Pseudarthrosis.—Bauer⁴⁷ recommended Kirschner's splintering method in the treatment for pseudarthrosis. He had had good results in the majority of the patients he had treated, although all the cases were of long standing and some had been subjected to previous operation without success. He moved and shifted the splinters about as the case demanded in order to peg the fragments, and when the nutritive conditions were particularly bad, he added autoplasmic fragments of bone from other parts of the body.

46. Whitman, A.: *J. Bone & Joint Surg.* **13**:122, 1931.

47. Bauer, K. H.: *Chirurg.* **19**:871, 1929.

In a discussion of the causes of pseudarthrosis, Koenig ⁴⁸ stated that he had frequently found soft tissue interposed between the fragments, and he thought that this was one of the chief causes of delayed union. On the other hand, union might take place in spite of interposition of soft tissues.

Bier ⁴⁹ maintained the view that mechanical factors played a subordinate part in producing delayed union. More important were faulty nutrition and chemical disturbances, especially the lack of hormones due to altered innervation. In such cases he relied on general rather than local treatment. In obstinate cases he employed Kirschner's bone splintering method.

Boehler ⁵⁰ recommended drilling many holes into the bone near the ends of the fragments, or the old method of refracturing recently again recommended by Goetze.

Skeletal Traction.—Fitzgerald, ⁵¹ describing the advantages and disadvantages of various methods of skeletal traction, pointed out that the use of the Kirschner wire was probably the most satisfactory in that with it there was less trauma and consequently less danger of infection than with ice tongs and Steinman's pin. Also the wire was more efficient. The technic of the use of Kirschner's wire was described.

Speed ⁵² advocated the use of steel pins of small caliber that could be driven through the bone and whose ends protruding through the skin could be covered with sterile dressings and embedded in plaster of paris casings, and thus serve to maintain position in fractures of the leg. The method necessitated previous complete reduction of the fracture, but the fixation was absolute and safe when the plaster had hardened.

[ED. NOTE.—We concur with Fitzgerald in respect to the advantages of Kirschner's wire over the ordinary skeletal pins and ice tongs. The patient is usually more comfortable, there is less risk of infection, and the wounds heal more promptly. We believe there are advantages in embedding pins in plaster casings when the fracture can be completely reduced. This method is particularly valuable in the treatment for fractures of the bones of the leg in that it provides complete immobilization, and this ought to be important in reducing the incidence of delayed union and non-union.]

Fractures of the Head and Neck of the Radius.—From the standpoint of treatment, Key ⁵³ divided fractures of the upper end of the radius

48. Koenig, F.: Deutsche med. Wchnschr. 56:939, 1930.

49. Bier: Deutsche med. Wchnschr. 56:939, 1930.

50. Boehler, F.: Deutsche med. Wchnschr. 56:939, 1930.

51. Fitzgerald, E. R.: Canad. M. A. J. 24:83, 1931.

52. Speed, K.: Surg., Gynec. & Obst. 51:854, 1930.

53. Key, J. A.: Treatment of Fracture of the Head and Neck of the Radius, J. A. M. A. 96:101 (Jan. 10) 1931.

into three groups: The first group consisted of those that ought to be treated conservatively, namely, fissure fractures of the head, chip or chisel fractures of the head in which the detached fragment comprised less than one third of the circumference of the head, and was not displaced or did not lie against the ulna, and fractures of the neck in which there was practically no displacement of the upper fragment. The second group consisted of fractures that ought to be treated by operation, namely, comminuted fractures of the head, chip or chisel fractures of the head in which a fragment larger than a third of the head was detached or displaced, or in which a small fragment was separated in close relation to the articulation with the ulna, and fractures of the neck in which the head was displaced downward or so tilted that its rounded border could no longer rotate in the sigmoid of the ulna and in which the displacement could not be reduced by manipulation. In the third group were those cases in which treatment should be conservative at first, and operation done later if necessary. This group included all doubtful cases of group 1, that is, cases with chip fractures of the neck with slight displacement, chip fractures with considerable displacement of the detached fragment which might be loose in the joint and fractures of the neck with complete and extensive displacement of the head which usually lay embedded in the tissues beneath the flexor muscles of the forearm and could no longer block motion at the elbow.

Fracture of the Capitellum.—Boehler ⁵⁴ pointed out the importance of distinguishing between the isolated fracture of the capitellum with forward displacement and rotation and the shearing off of the articular cartilage of the capitellum with posterior displacement. The former lesion was encountered only in persons with a hyperextensible elbow; the latter only in persons with a valgus elbow. These lesions could therefore be produced only when there were proper preexisting constitutional conditions. They should be differentiated from other fractures of the lower end of the humerus.

Traumatic Myelitis Resulting from Fractures of the Spine.—Gurdjian ⁵⁵ studied seventy-two cases of fractured spine with transverse myelitis. The cord injury was produced by either direct or indirect violence, i. e., either due directly to pressure from the bony vertebral column or simply by concussion. Central softening of the cord was a frequent finding in fractured spines, and might extend up the cord for some distance from the site of injury. The fractures were either compression or chip fractures of the bodies of the vertebrae. Of thirty-two compression fractures, nineteen were lumbar, seven were dorsal and six were in the cervical spine. Careful technic should be exercised in obtain-

54. Boehler, L.: Arch. f. Orthop. 28:734, 1930.

55. Gurdjian, E. S.: Am. J. Roentgenol. 25:65, 1931.

ing good anteroposterior and lateral roentgenograms, particularly of the cervicodorsal junction, a not infrequent site of fracture.

Fractures of the Pelvis.—Nineteen cases of fracture of the pelvis were reviewed by Parker.⁵⁶ They constituted 3 per cent of all fractures observed. The author found that the gravity of the injury depended on the amount of damage to the structures within the pelvis. There were two deaths from shock. The injury was produced in most cases by a rolling or squeezing force or by an automobile crush. A few cases were caused by a severe fall. The common associated injuries were ruptured bladder, ruptured urethra, ruptured kidney and fractures other than those of the pelvis. After examination for complications the patients were placed flat in bed and the position maintained with sandbags to the legs and pelvis. In a few cases traction and abduction were used where there was marked upward displacement of the ilium. A pelvic belt was used when there was separation of the sacro-iliac joint or symphysis pubis. The average stay in the hospital was thirty-nine days. Good functional results were obtained in thirteen cases.

Fracture of the Bones of the Leg.—Kennedy⁵⁷ presented a study of 114 patients with fractures of the bones of the leg, who had been treated at the Beekman Street Hospital between 1924 and 1929. Many of them were severe compound fractures. The favorite form of treatment in most cases was skeletal traction by means of Steinman's pin through the os calcis with the leg suspended in a Thomas splint. Fixation in plaster was employed primarily in 70 patients, but in 14 proved unsatisfactory and had to be abandoned in favor of skeletal traction. Operation was avoided as much as possible, the danger of tetanus being considered real because of the frequent contamination of the skin with horse manure. The Massachusetts General Hospital system of rating the end-results at the end of one year on the basis of the anatomic, functional and economic results was employed.

[ED. NOTE.—The article represents a thorough study and deserves to be read. The results obtained are a recommendation for the methods of treatment used.]

DISLOCATIONS

Disruption of the Pelvis with Luxation of the Innominate Bone.—Eight cases of luxation of the innominate bone were reported by Peabody.⁵⁸ The displacement was associated in each case with a fracture of the pelvic ring or separation of the symphysis pubis. One of these patients

56. Parker, O. W.: Minnesota Med. 14:29, 1931.

57. Kennedy, R. H.: Ann. Surg. 93:563, 1931.

58. Peabody, C. E.: Disruption of Pelvis with Luxation of Innominate Bone, Arch. Surg. 21:971 (Dec.) 1930.

died immediately, one could not be traced, and the others completely recovered. The injury was produced either by a fall, or by a crushing or twisting force acting on the pelvis. Visceral complications were rarely seen. Severe sciatica was observed only in patients with an accompanying fracture of the fifth lumbar vertebra. Treatment was traction on the leg of the involved side under anesthesia followed by manipulation with the aid of the fluoroscope. After reduction a webbing belt was tightly applied around the pelvis and the patient placed on a Bradford frame with traction on the leg of the injured side. In two cases rotary redisplacement required wiring of the symphysis pubis. Ankylosis of the involved sacro-iliac joint occurred in all of the cases followed.

Chronic Subluxation of the Distal Radio-Ulnar Joint.—Berry⁵⁹ reported the case of a youth, aged 20, who after a Colles' fracture was unable to resume his work as a carpenter, owing to undue anteroposterior mobility of the lower end of the ulna on the radius. Quite slight pressure on the palm of the hand would cause the head of the ulna to project backward. Berry, therefore, fused the distal radio-ulnar joint by removing the opposing cartilaginous surfaces and driving a bone peg through the ulna into the radius, and at the same time resected 1 inch (2.5 cm.) of the ulna in its lower fourth. Following the operation, the patient was able to resume his work and even to mix concrete with a shovel. Supination and pronation were perfect.

[ED. NOTE.—Berry's method of dealing with chronic subluxation of the distal radio-ulnar joint deserves consideration. It is not as simple as fixation of the head of the ulna to the radius by fascial suture, but it may be more positive in its results. The result achieved in this single case merits further trial of the method.]

RESEARCH

The Rôle of the Macrophage in Absorption from Synovial Cavities.—Rynearson⁶⁰ studied the absorption of various dye substances from the synovial cavities of dogs. He observed that the rôles played by the secretory cells and by the macrophages were different. The former were penetrated only by colloid substances, whereas the macrophages absorbed the particulate matter. While the colloid substances and fluids were carried away through the blood and lymph, the dye-stained macrophages were found in the case of the knee joint chiefly in the inguinal and lumbar lymph nodes and spleen. These observations suggested to the author that in arthritis the toxic substances might be absorbed by the secretory cells and that they were therefore carried to various parts of

59. Berry, J. A.: Brit. J. Surg. **18**:526, 1931.

60. Rynearson, E. H.: J. Bone & Joint Surg. **13**:127, 1931.

the body, whereas bacteria were transported only by the macrophages and carried to the lymph nodes.

[15b. NOTE.—Investigators in general have not been able to distinguish a true secretory type of cell in the synovial membrane and hence there may be some disagreement with this part of the author's conclusions.]

Influence of Alterations in Circulation on Repair of Bone.—Pearse and Morton,⁶¹ in previously reported experiments, demonstrated that venous stasis accelerated bone repair. They carried their experiments further and found that in dogs obstruction of the lesser saphenous vein did not accelerate healing of the fractured fibula, probably because of the extensive anastomosis between this vein and the great saphenous vein. Obliteration of the femoral artery was found to delay healing, whereas lumbar sympathectomy had little effect on osteogenesis.

Fate of Transplanted Cortical Bone.—Davison and Kraff⁶² attempted to determine the viability of autoplasmic cortical bone grafted into cortical bone. Two dogs from the same litter were used for each experiment. One dog was fed sodium alizarin sulphonate which colored all new formed bone red from weaning until the dog was killed. A cortical graft from the temporal bone was transplanted from the dog given sodium alizarin sulphonate to the other dog and vice versa. The authors found that cortical bone transplanted aseptically and with perfect mechanical adaptation and fixation healed by primary intention and remained alive.

Regeneration of Hyaline Cartilage.—From a series of experiments on dogs, Shands⁶³ concluded that regeneration of hyaline cartilage might occur after injury. No regeneration was noted in less than four weeks. The various stages of repair were as follows: fibrin, granulation tissue, connective tissue, cartilage cells in connective tissue, fibrocartilage and new hyaline cartilage. No difference was found in the regenerative power of the cartilage in different areas of the joint. No definite evidence of a perichondrium was found. Direct trauma to the hyaline cartilage occasionally caused a proliferation of nests of new cartilage cells.

Myostatic Contracture Following Tenotomy.—Davenport and Ranson⁶⁴ studied the changes in the gastrocnemius muscle after tenotomy of

61. Pearse, H. E., and Morton, J. J.: J. Bone & Joint Surg. **13**:68, 1931.

62. Davison, C., and Kraff, A.: Fate of Cortical Bone Graft, Arch. Surg. **22**: 94 (Jan.) 1931.

63. Shands, A. R.: Regeneration of Hyaline Cartilage in Joints: Experimental Study, Arch. Surg. **22**:137 (Jan.) 1931.

64. Davenport, H. K., and Ranson, S. W.: Contracture Resulting from Tenotomy, Arch. Surg. **21**:995 (Dec.) 1930.

the tendo achillis in cats and rats. They pointed out that other observers had demonstrated that if the bony attachments of a skeletal muscle were left immobilized for several days so as to prevent the changes in length that normally resulted from spontaneous and reflex movement there occurred a fixation of the muscle at the length thus imposed on it. If taken early, this contracture could be overcome by active or passive movement, but if left untreated for some time the damage might become irreparable. This process called myostatic contracture by Davenport and Ranson was dependent on intact innervation. After it had developed, however, it persisted even after section of the motor nerve. According to the authors, it was an abnormal manifestation of tonic contraction. A muscle affected by this condition could not extend normally or contract normally.

Studying the myostatic contraction produced by tenotomy of the tendo achillis, the writers found an increase in the diameter of the muscle fibers, a more pronounced longitudinal fibrillation, blurred cross-striations, a dissociation of the membranes holding the myofibrils in alignment, a wavy contour in some of the fibers, light and dark irregularly outlined bands and an increase in the nuclei of the wandering cell type. There was no evidence of increase of the connective tissue elements. A 20 per cent loss in weight was found in the gastrocnemius muscle.

CORRECTION

In the article by Drs. Karl H. Martzloff and George E. Burget, entitled, "The Closed Intestinal Loop: III. Aseptic End-to-End Intestinal Anastomosis and a Method for Making a Closed Intestinal Loop Suitable for Physiologic Studies," in the July issue (23:26, 1931), an error occurred in the references at the bottom of page 29; reference 3 has been repeated and the first line of reference 5, omitted. These two references should read:

3. Rostowzew, M. I.: Aseptische Darmnaht, Arch. f. klin. Chir. 82:462, 1907.
5. Rankin, F. W.: An Aseptic Method of Intestinal Anastomosis, Surg., Gynec. & Obst. 47:78, 1928.

THE NATURE AND ORIGIN OF SYNOVIAL FLUID*

DAVID H. KLING, M.D.

Frederick Brown Orthopedic Research Fellow

NEW YORK

The conception of the synovial membrane as an endothelium or epithelium designed to secrete the synovial fluid was challenged by Hueter¹ in 1866. By the method of silver impregnation he demonstrated interspaces between the synovial cells filled by collagenous fibers which, in some places, covered the upper surface of the membrane. After thirty years of controversy, Hueter's views were brought to general recognition by Braun² and Hammer.³ The majority of recent investigators regard the synovial membrane as a modified connective tissue. This theory, however, makes the origin of the synovial fluid problematical. Of the various explanations advanced, none is supported by sufficient evidence.

This study deals with the phenomena of precipitation, the viscosity, the specific gravity and the mucinous substance of synovial fluids. Different fractions were separated and analyzed. By correlation of the data, an effort was made to determine the source and composition of the synovial fluid. Some clinical applications are outlined.

1. PRECIPITATION PHENOMENA (SACK FORMATION)

A simple test to differentiate between transudates and exudates was devised by Primavera and Rivalta.⁴ A drop of the unknown fluid is permitted to fall into a test tube with 3 per cent acetic acid. Plasma and transudates cause a faint trace while exudates produce a turbidity like cigaret smoke, which is regarded as a positive reaction. Effusions

* Submitted for publication, Dec. 30, 1930.

* Read in part before the Pathological Conference, Oct. 24, 1930.

* From the services of Dr. Harry Finkelstein and Dr. Samuel Kleinberg, Hospital for Joint Diseases.

1. Hueter: Zur Histologie der Gelenkflächen und Gelenkapseln mit einem kritischen Vorwort über die Versilberungsmethode, *Virchows Arch. f. path. Anat.*, 1866, vol. 36.

2. Braun, H.: Untersuchungen über den Bau der Synovialmembran und Gelenkknorpel sowie über die Resorption flüssiger und fester Körper aus der Gelenkhöhle, *Deutsche Ztschr. f. Chir.*, 1894, vol. 39.

3. Hammer, J.: Ueber den feineren Bau der Gelenke, *Arch. f. mikr. Anat.* 43:266 and 813, 1894.

4. Primavera and Rivalta, in Sahli: *Diagnostic Methods*, ed. 2, Philadelphia, W. B. Saunders Company, 1918, p. 917.

of the pleural and peritoneal cavities and the contents of hydrocele and serous ovarian cysts give either a positive or a negative Rivalta reaction (fig. 1, tubes *b* and *e*).

Normal and the great majority of pathologic synovial fluids, however, behave differently. The drop does not disperse immediately in the acid solution, but forms a membrane that envelops the contents like a sack (fig. 1, tubes *a*, *c* and *d*). This formation may float on the surface like a balloon, or sink to the bottom of the test tube. A great number of synovial fluids form a sack that sinks to a certain depth and is connected by a tube to the surface. The membrane can be very resistant, in which event the sack is permanent. Figure 2 shows a sack

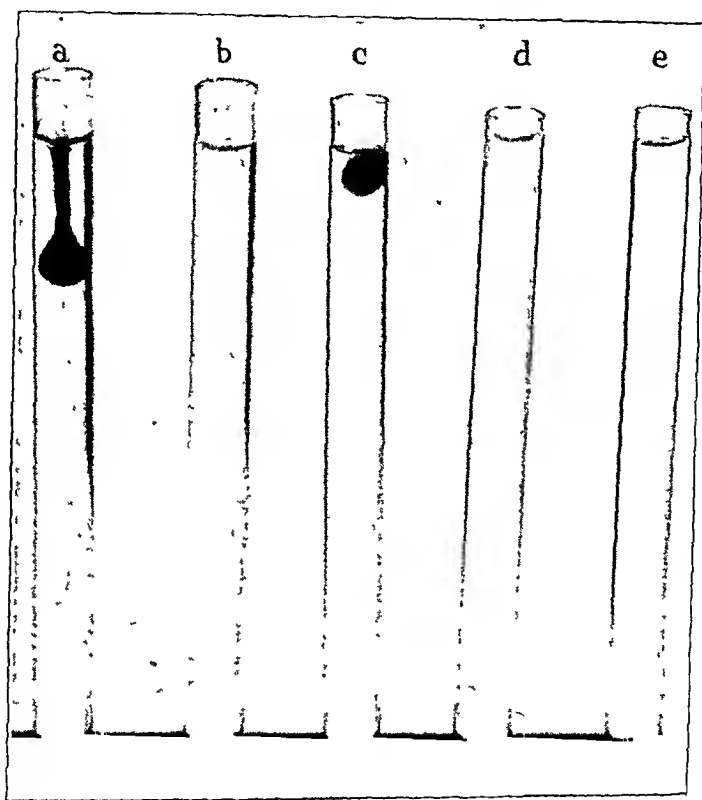


Fig. 1.—*a* and *c* show sack and tube formation; *b*, streaks of turbidity; positive Rivalta reaction in a pleural effusion; *d*, a very thin sack in synovial fluid, and *e*, perfectly clear fluid; negative Rivalta reaction in a serous ovarian cyst.

preserved for months. Other fluids form thin membranes through which diffusion takes place rapidly and which disappear in a short time. The diffusion of hemoglobin into the acid can be nicely observed in hemorrhagic fluids. When the acid solution diffuses into the sack, a secondary membrane is sometimes formed.

The behavior of the sack depends on the concentration of the acid used and the character of a given fluid. Table 1 gives a summary of the conditions of sack formation in various concentrations of acetic and hydrochloric acid. The former causes sacks to form in concentrations

from glacial to 0.25 per cent, in the latter, in from twentieth-normal to two hundredth-normal solutions.

Table 2 shows that a maximum dilution of 1:10 with water still can result in sack formation. With serum, the maximum dilution was 1:4. Water tends to keep the sack on the surface, while serum, owing to its higher specific gravity, favors falling and dispersion. This will explain differences when, later, saliva and synovial fluid are compared.

TABLE 1.—*Sack Formation in Acids*

Acid	Characteristics
Glacial acetic.....	Unstable, quickly torn
50% acetic.....	Thin, swims on surface
50 to 5% acetic.....	Remains on surface
5 to 1% acetic.....	Sack and tube formation
1 to 0.25% acetic.....	Thin, stringy tubes
Concentrated to tenth-normal hydrochloric acid (0.001%).....	No sacks
Twentieth-normal hydrochloric acid.....	Sack sinks to bottom
Fortieth-normal hydrochloric acid.....	Sack floating, then sinking
Eightieth to two hundredth-normal hydrochloric acid.....	Tube formation
Two hundredth-normal hydrochloric acid.....	No sack formation

TABLE 2.—*Maximal Dilution of Ten Synovial Fluids with Water and Serum Giving Sack Formation*

		Cases
Dilution with water.....	1:3	1
Dilution with water.....	1:5	6
	1:10	3
Dilution with serum.....	4:6	1
	1:1	1
	1:4	1

TABLE 3.—*Sack Formation in Effusions from Two Hundred Joints (One Hundred and Twenty-Two Inflammatory and Seventy-Eight Traumatic) and in Fluids from Thirteen Normal Knee Joints at Autopsy or Operation*

	Pathologic Fluids		Normal Fluids	
	Cases	Per Cent	Cases	Per Cent
Sack formation: positive.....	188	94	13	100
negative.....	12	6	0	0
Rivalta reaction: positive.....	8	4
negative.....	4	2

Sacks were produced in the original fluids as well, but they were extensively studied in the clear filtrate after separation of cellular sediment by centrifugation.

Table 3 gives a review of my studies on sack formation. Fluids obtained from thirteen normal joints following amputation or at operation were positive for sack formation. In the effusions of two hundred inflammatory and traumatic joints, sack formation was present in 94 per cent and absent in only 6 per cent. Of the latter, 4 per cent gave positive and 2 per cent negative Rivalta reactions.

In the twelve cases in which sacks did not form, the following diagnosis was made: chronic prepatellar bursitis (housemaids' knee), seven cases; chronic nonspecific arthritis, four cases (one of these fluids was obtained at operation, and it is likely that there was an admixture of serum), and ganglion of the wrist, one case (this fluid was aspirated previously and contained numerous cells, with 90 per cent polymorphonuclear leukocytes).

Sacks Containing Acid in the Synovial Fluid.—By reversing the arrangement of the experiment, membranes can be produced which enclose the acid solution. A small test tube is half filled with synovial fluid; a drop of methyl orange is added. Most synovial fluids, being

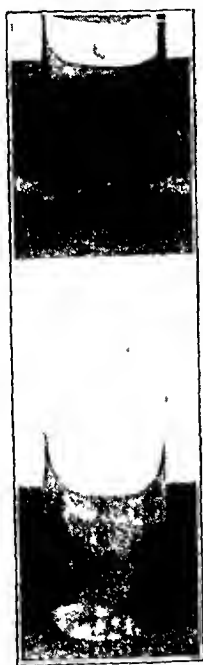


Figure 2



Figure 3

Fig. 2.—Sack which has been preserved for two months is seen floating at the top of the tube.

Fig. 3.—Sack and tube containing hydrochloric acid which was dropped into synovial fluid.

slightly alkaline, take a yellow tint by this indicator. Several drops of 10 per cent hydrochloric acid are let fall into the tube. The specific gravity of the acid at this concentration is around 1.050 and exceeds the gravity of synovial fluids, as shown in table 11. The hydrochloric acid therefore sinks, enveloped in a membrane which forms a tube and a sack at the bottom. While the rest of the fluid remains yellow, the contents of the tube and the sack change to red, which proves that they contain the hydrochloric acid. When the tube is allowed to stand, diffusion takes place through the membrane. This causes the sack to rise to a higher level. and finger-like protusions branch out from it (fig. 3). Gradually the

distinct structures disappear and a loose meshwork fills the tube. The binding of acid is permanent. The contents never take the red color observed in plasma, transudates and exudates. In these fluids, the acid sinks freely, the whole fluid changes quickly to red, and a pinkish precipitate accumulates at the bottom.

The precipitation of synovial fluid by alcohol also has a characteristic appearance. A drop of synovial fluid let fall into a tube with absolute alcohol sinks to the bottom leaving threads throughout the fluid and a mushy precipitate at the bottom (fig. 4). which looks like a bulb and



Fig. 4.—Mushy precipitate produced by dropping synovial fluid into absolute alcohol.

roots, and represents an effort at sack formation, prevented by the excessive dehydrating action of the alcohol. No changes occur if the tube is allowed to stand for weeks. Serum, transudates and exudates form a precipitate which falls quickly to the bottom, the alcohol remaining clear.

Sack formation is also observed when a drop of synovial fluid is let fall into a concentrated solution of corrosive mercuric chloride; sacks containing the sublimate solution are obtained by dropping the corrosive mercuric chloride into the synovial fluid.

Microscopic Appearance.—Under low magnification the membranes appear to consist of bundles and threads running in different directions and forming a meshwork. Under high magnification, minute granules are seen to fill the meshes. The structures resemble the inner shell of a hen's egg.

Comment.—On the basis of the conception of the synovial membrane as a connective tissue, the theory was widely accepted that synovial effusions are derived from the circulation.

This study of precipitation, however, has demonstrated peculiar precipitation phenomena differing from the reactions that occur in either transudates or exudates. Not only most effusions from inflammatory joints, but even the hemorrhagic effusions are positive for sack

TABLE 4.—Comparative Reactions of Blood Serum, Synovial Fluid, Egg White and Saliva to Precipitation by Various Agents

Reagent	Serum	Synovial Fluid	Egg White	Saliva
Water.....	Clear	Clear	Turbid	Clear
Acetic acid.....	Precipitation	Sack	Sack	Sack
Hydrochloric acid.....	Precipitation	Sack formed between 20th and 200th normal hydrochloric acid	Sack	Sack
Hydrochloric acid 10% overlaid.....	Precipitation	Sack	Sack	Sack
Alcohol.....	Granules	Threads
Alcohol overlaid.....	Precipitation at border	Precipitation
Nitric acid.....	Precipitation	Precipitation	Precipitation	Precipitation
Boiling.....	Curd	Curd	Curd	Turbid
Potassium hydroxide.....	Clear	Clear	Jelly	Clear

formation. They therefore do not consist simply of blood corpuscles and plasma, but must contain at least one component not derived from the circulation. This substance that produces the characteristic precipitation phenomena is, on the other hand, also present in normal synovial fluids.

The next step in this investigation was a search for other body fluids which give identical precipitation reactions.

Sack formation was found to be positive in saliva and egg white. The sacks in both of these substances swim on the surface of the 3 per cent acetic acid solution and are transparent. Table 4 gives a review of the comparative reactions. Both saliva and egg white are products of cell secretion and not of extravasation. Both are viscous fluids containing a mucinous substance. Synovial fluids have similar properties. The study of viscosity and the mucinous substance was therefore undertaken.

2 VISCOSITY

Data on the viscosity of synovial fluids have been recorded only by Schneider⁵ and by Cajori and collaborators.⁶ I shall therefore analyze and compare my material with the observations of these authors and then follow up clues uncovered by this study which may lead to the source of synovial fluid.

The specific or relative viscosity was determined in seventy fluids from sixty-five patients (table 5). Fifty specimens were aspirated from inflammatory effusions in forty-seven cases of acute and chronic specific and nonspecific monarticular or polyarticular arthritis and bursitis. The diagnosis was made on the basis of clinical findings, roentgenograms, bacteriologic, serologic and cytologic studies and estimations of bilirubin in the fluids.

Twenty fluids of traumatic origin were obtained from eighteen patients. The history of injury was confirmed by the hemorrhagic

TABLE 5.—*Summary of Determinations on the Viscosity of Synovial Fluid*

Joints	Inflammatory Cases*	Traumatic Cases†
Knee..	38	18
Prepatellar bursitis	4	4
Ankle.	2	1
Wrist.	2	0
Elbow	1	0
Total.	47	18

* One case was aspirated three times and one twice.

† Two cases were aspirated twice.

character, the presence of fat and bone marrow cells or the high icteric index of the effusions, as I have pointed out in a series of papers.⁷ The viscosity was determined on centrifugated clear fluids, with but one exception. This effusion was aspirated from a patient with tuberculous arthritis of the knee. It was milky, contained débris and did not separate on prolonged centrifugation. The viscosity was 18.

The Hess viscosimeter was used, which permits the determination of viscosity up to twenty-eight times that of water at room temperature.

5. Schneider, J.: Untersuchungen über die Viskosität menschlicher Synovia, *Biochem. Ztschr.* **160**:325, 1925.

6. Cajori, F. A.; Crouter, C. Y., and Pemberton, R.: The Physiology of Synovial Fluid, *Arch. Int. Med.* **37**:92 (Jan.) 1926. Cajori, F. A., and Pemberton, R.: Chemical Composition of Synovial Fluid in Cases of Joint Effusion, *J. Biol. Chem.* **76**:471, 1928.

7. Kling, D. H.: Fat in Traumatic Effusions of the Knee Joint, *Am. J. Surg.* **6**:71, 1929; Bilirubin in Effusions of the Joints, *Arch. Surg.* **20**:17 (Jan.) 1930; Erythroblasts and Myelocytes in Traumatic Effusions of the Knee Joint, *Am. J. Surg.* **7**:824 (Dec.) 1929; Wassermann Reaction in Joint Fluids, *Am. J. Syph.* **13**:596, 1929.

Fluids of a higher viscosity had to be diluted with distilled water. The influence of dilution and the accuracy of the apparatus will be discussed later.

Analysis of the Material.—Fluid was aspirated from the knee joint in 78.5 per cent of the cases (table 5). The viscosity varied in inflammatory effusions from 1.6 to 72 and in traumatic effusions from 2.6 to 34 (table 6). This exceeds by a wide margin the range of viscosity of transudates or exudates and normal secretory products like saliva and egg white (table 7). The largest variation (table 10) is seen in chronic nonspecific arthritis (from 1.6 to 72), and the next largest in syphilitic arthritis (from 4.5 to 40.5). Comparatively smaller is the range for gonorrheal arthritis (from 10.1 to 16.8) and tuberculous arthritis (from

TABLE 6.—*Specific Viscosity at 20 C.*

Viscosity	Inflammatory Effusions, Number Fluids	Traumatic Effusions, Number Fluids
1.6 to 5.....	5	2
5 to 10.....	6	7
10 to 20.....	22	6
20 to 30.....	8	4
30 to 40.....	3	1
40 to 50.....	4	0
50 to 72.7.....	2	0
Total.....	50	20

TABLE 7.—*Viscosity, Specific Gravity and Sack Formation of Synovial Fluids*

	Num- ber	Specific Viscosity				Specific Gravity	Sack:
		1.6 to 5	5 to 10	10 to 20	Over 20		
Inflammatory.....	50	5	6	22	17	1.018 to 1.032	Positive 44 Negative 6
Traumatic.....	20	2	6	7	5	1.015 to 1.026	Positive 19 Negative 1

16.6 to 24). One case of rheumatic fever and one of purulent arthritis showed that the viscosity varies at different aspirations during short intervals (from five to seven days) in the same joint.

In the series of traumatic effusions, the cases of prepatellar bursitis showed a smaller range (from 7.9 to 16.1) than the fluids from the knee joints, and two intra-articular fractures showed less variation but higher viscosity (from 13.2 to 22).

Review and Discussion of the Literature.—Schneider devoted his study, published in 1925, to the determination of the viscosity of normal synovial fluid. He aspirated fluid from twenty-nine knee joints of patients who had died from various acute and chronic diseases. Only two showed effusion. He constructed an elaborate apparatus which permitted the examination of minute amounts of the fluid and which registered the highest degrees of viscosity. In the twenty-seven cases

of apparently normal joints, he found a viscosity of from 3.9 to 1,490. Of the two effusions, the viscosity in a case of purulent arthritis was 275.3, and in a case with joint mice, 33.3. The only fluid examined from a living patient was obtained in a case of osteochondritis dissecans; the viscosity was 22.7. The viscosity was highest in cases of sudden death and lower after chronic wasting diseases which had kept the patients in bed, especially tuberculosis, cancer and circulatory disorders. This, Schneider explained by the assumption that resorption of water decreased in the latter cases and by referring to the analysis of synovial fluids of cattle published by Frerichs⁸ in 1846. The latter found that the content of solids was about 40 per cent lower and that of water greater in the synovial fluids of new-born calves and fatted cattle than in the synovial fluids of grazing oxen.

TABLE 8—*Viscosity, Specific Gravity and Sack Formation of Various Fluids*

Fluid	Number	Range of Variation	Viscosity	Specific Gravity	Sack
Normal joint	1		20.00	...	Positive
Normal joint	1		10.70		Positive
Saliva, filtered	5	± 0.20	1.90	1.005	Positive
Saliva, full	2	3.75		Positive
Egg white	4	+1.55 -0.95	5.25	1.040	Positive
Plasma.	2	± 0.20	2.30	1.027	Negative
Serum .	10	+0.50 -0.80	1.90	1.018	Negative
Serum from ovarian cyst	2	+0.80 -0.70	2.20	1.020	Negative
Lymph vesicle in skin	1		2.10	1.012	Negative
Peritoneal	1		1.60		Negative
Pleural	1		1.90	1.022	Negative

On the basis of his observations at autopsy, Schneider estimated that normal synovial fluids have a range of viscosity between 500 and 1,500. Extraordinary as these figures may appear, another observation is still more surprising. He induced the evaporation of 5 per cent of the water content of a fluid, and the viscosity rose from 1,490 to 3,659, an increase of nearly 150 per cent. If that be true, a dilution of 1:1 would depress the viscosity about 3,000 per cent. As has been mentioned, my procedure was to dilute fluids of a viscosity over 28 and to multiply the reading by the volume of water used.

Control examinations were therefore carried out on a series of fluids that had a viscosity under 28. After determination of the viscosity, the fluids were diluted, and the viscosity was registered and multiplied by the volumes of water used. The results in diluted fluids were plus or minus 4.5 per cent; table 9 gives two estimations. The influence of evaporation was also controlled up to 35 per cent. The maximum

⁸ Frerichs, T. Die Synovia, in Wagner, R. Handwörterbuch der Physiologie, 1846, pt. 3, p. 463.

increase over the expected value was 26 per cent. The figures are in good agreement with the experimental curve of the increase of viscosity by protein solutions within the concentrations in synovial fluid, which is given by Hatschek.⁹ I have therefore concluded that this calculation is correct within these limits of error, and that the Hess apparatus can be used in a comparative study of the viscosity of synovial fluids. It offers the advantage of having been widely employed in estimations of the viscosity of blood. Less than 0.5 cc. of fluid is needed. The instrument is reasonably priced and comparatively simple to operate. Schade¹⁰ justly pointed out the danger of using new and untried constructions for the determinations of viscosity.

A few precautions are to be observed in carrying out the test. The apparatus should be frequently checked, water in both sides of the capillary being used. The flow of the fluids should be smooth. It is advisable first to work with fluids of low and stable viscosity, for

TABLE 9.—*Effect of Dilution and Evaporation on Viscosity*

Fluid	Viscosity	Per Cent	Difference*
Full fluid I.....	12.2	100
Diluted 1:1.....	5.6	46	— 4
Full fluid II.....	6.2	100
Diluted 1:1.....	3.4	55	+ 5
Evaporation 5%.....	7.2	116	+11
Evaporation 10%.....	8.0	130	+20
Evaporation 20%.....	8.8	142	+22
Evaporation 35%.....	10.0	161	+26

* Difference between expected and obtained viscosity.

instance, with serum. Several determinations should be taken on one fluid, and the average value registered. If the variation exceeds 15 per cent, the apparatus must be cleaned and the water changed and rechecked. For the dilution of synovial fluid, distilled water of room temperature should be used. One per cent is added to the result for each degree above, and subtracted for each degree below, 20 C.

In only two instances in which the joint appeared to be normal did I obtain enough fluid to determine the viscosity. One fluid was secured at operation on a man, 20 years of age, who had suffered from an injury to the internal meniscus a year previously. The viscosity was 20. The second fluid was aspirated from the knee of a leg, amputated for a chronic ulcer after a burn, in a patient 21 years of age. The viscosity was 10.7. The fluids had the same appearance and sack formation as did those from the other ten normal knee joints that I examined at autopsy. Some of the effusions of high viscosity, especially the contents of ganglions, appeared decidedly thicker and more viscid than the

9. Hatschek, E.: *Viscosity of Liquids*, London, G. Bell & Sons, 1928.

10. Schade, H.: *Die physikalische Chemie in der inneren Medizin*, ed. 3, Leipzig, Theodor Steinkopff, 1922, p. 562.

material obtained at autopsy. If conclusion is permitted from these cases, I would range the viscosity of normal fluid well within the limits found for the effusions and the two determinations just cited.

Cajori and his associates⁶ examined the viscosity of pathologic effusions with the Hess apparatus. Their data, recorded in two papers, can therefore be directly compared with my material. In an article on the physiology of the synovial fluid that appeared in 1926, Cajori, Crouter and Pemberton gave the viscosity in nine cases. One fluid was from a patient with traumatic synovitis; viscosity 3.3. The remaining eight were obtained from cases of chronic arthritis, the etiology of which could not be defined. The viscosity varied from 2.7 to 16.7. The authors did not comment on their observations. These data are in agreement with my material. Even in so limited a number, the wide range of variation exceeds decidedly the limits of transudates, exudates and other secretions. In the second paper, by Cajori and Pemberton, in which the chemistry of the synovial fluids is dealt with, the viscosity in twelve effusions is registered. One fluid (case 10) was from a patient with villous arthritis, and had a viscosity of 4.78; another (case 5) was from a patient with anasarca, and had a viscosity of 4.71. No diagnosis was given in the remaining ten cases, which had a range of viscosity between 2.91 and 4.79. The difference between the maximum and minimum viscosity was only 1.88 and forms a contrast to the extremely high values of Schneider. The authors calculated an average viscosity of 4, next to their average for plasma. This is apt to be misleading. Simple observations show the wide difference in fluidity and stickiness of fluids within joints which is not commonly met with in plasma. Here an average represents a nearly uniform property. In the fluids of joints, however, it only indicates an artificial condition caused by a limited selection of the material, most likely owing to a mistake in the technic of aspiration. It is frequently noticed that thin needles are used. Therefore, only effusions of low viscosity are obtained; when the fluid is thick, the aspiration will not be successful. This also explains why some physicians, after attempting without success to aspirate traumatic effusions, maintain that the blood is coagulated in the synovial cavities, while really only small coagula form, and the bulk of the blood remains fluid but of thick consistency through an admixture of synovial secretion. It is therefore essential to employ thick needles in aspirating fluids from joints.

Factors Responsible for Viscosity.—The degree of inflammation and the stage of the process are of importance, irrespective of etiology. For this reason fluids from patients with acute specific and nonspecific arthritis show less variation and start from a higher level than effusions from patients with chronic disease (table 10). In the four cases of gonorrheal arthritis showing the smallest variation, the fluids were aspi-

rated within five weeks after the onset of symptoms. The lowest values were found in chronic hydrops, without involvement of the structures of the joints, and the highest were registered in hypertrophic arthritis and thickened bursae when only a few cubic centimeters of fluid was obtained. Roentgenograms confirmed the fact that no further accumulation of fluid was present in these cases.

The influence of these factors was pronounced in the group of syphilitic cases. Although of uniform etiology, they were in different stages. The lowest viscosity of 4.5 was found in a child, 5 years of age, with congenital syphilis, in whom effusion of the knee joints had developed two weeks previous to examination. Thirty cubic centimeters of fluid was aspirated from each joint. The highest viscosity, 40.8, was found in a case of dactylitis and tenosynovitis of the wrist of two years' duration which yielded only 2 cc of fluid. Another case of

TABLE 10—*Relation of Viscosity to Types of Arthritis*

Inflammatory	Cases	Viscosity	Traumatic	Cases	Viscosity
Nonspecific arthritis, acute and subacute*	11	12 to 32	Synovitis, knee	11	2.6 to 34
Chronic†	22	1.0 to 72	Intra articular fracture, knee	2	13.2 to 22
Syphilitic	5	4.5 to 40.8	Prepatellar, bursitis	4	7.9 to 10.1
Tuberculous	3	16.6 to 24	Synovitis, ankle	1	20
Gonorrheal	4	10.1 to 16.8			
Rheumatic fever (3 determinations)...	1	7.8 to 12			
Purulent arthritis (Staphylococcus aureus, positive; 2 determinations)	1	6 to 16.2			

* Streptococcus positive in four cases

† Streptococcus positive in three cases, and staphylococcus positive in one case

syphilitic hydrops of the right knee, of thirteen years' duration, from which 50 cc. of fluid was obtained, showed a viscosity of 11.4.

The wide range of viscosity points to differences in the physico-chemical composition of synovial fluid in need of investigation.

3 SPECIFIC GRAVITY

The specific gravity of body fluids is determined by the concentration of crystalloids and colloids. According to Ruess,¹¹ the specific gravity of plasma and that of effusions is approximately proportional to their content of proteins.

This same relation was found also by Horyi,¹² in twenty-five synovial fluids obtained at autopsy on patients with general edema due to disorders of the circulation and kidneys. The specific gravity varied from 1.003 to 1.818. The lowest specific gravity was associated with an albumin content of about 0.5 per cent, and the highest (1.018) with

11. Ruess, cited in Sahli. *Diagnostic Methods*, ed 2, Philadelphia, W. B. Saunders Company, 1918, p 917.

12. Horyi, K: Ueber die menschliche Synovia, *Virchows Arch. f. path. Anat.* 251:649, 1924.

one of 3.9 per cent. For normal synovial fluids, a specific gravity of 1.040 was given by Mayeda.¹³ He did not state the number or source of the fluids.

In only three cases of effusions into the joints was the specific gravity registered. In two cases of synovitis of the knee, Hammarsten¹⁴ found a specific gravity of 1.017 and 1.022, respectively. In a case of coxitis, Salkowski¹⁵ registered a value of 1.021.

I tested twenty-five inflammatory and fifteen traumatic effusions for specific gravity. When sufficient fluid was at hand the estimation was carried out with the urinometer; otherwise, a modification of Hamerschlag's drop method in the determination of the specific gravity of blood was used (Kirkpatrick and Kling¹⁶). A water-insoluble mixture with a specific gravity of 1.020 is made up by combining one part of carbon tetrachloride and three and a half parts of xylene in a test tube. A drop of synovial fluid is let fall into the mixture. If it sinks to the

TABLE 11.—*Specific Gravity*

Specific Gravity	Inflammatory Effusions		Traumatic Effusions	
	Cases	Per Cent	Cases	Per Cent
1.015 to 1.020	7	28	5	33.5
1.021 to 1.025	13	52	8	53.5
1.026 to 1.030	4	16	2	13.4
1.032	1	4	0
Total	25		15	

bottom, its specific gravity is higher, and the heavy carbon tetrachloride is added slowly until the drop is fixed about midway in the fluid. If the drop floats on the surface, the specific gravity is depressed by the addition of the lighter xylene until it again comes down half way.

Over 50 per cent of both groups had a specific gravity between 1.021 and 1.025 (table 11). These values are also commonly found in exudates. About 30 per cent showed lower values and were in the range of those for serum or transudates. Only about 15 per cent had a gravity over 1.025, but they did not exceed the values for plasma. The striking differences in viscosity were therefore not reflected by the specific gravity. There was no correspondence between these properties; the

13 Mayeda, Tomosuke: Experimentelle histologische Studie über die Synovialmembran, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo **21**:393, 1919-1920.

14 Hammarsten, O.: Beiträge zur Chemie der Synovia, Jahresb. Thier-Chemie **12**:480, 1881-1882.

15 Salkowski, E.: Zur Kenntnis der Synovia, insbesondere des mucinulicher Körpers derselben, Virchows Arch. f. path. Anat. **131**:304, 1893.

16 Kirkpatrick, J., and Kling, D. H.: A Simplified Method for Determination of the Specific Gravity of a Few Drops of Urine, J. A. M. A. **87**:487 (Aug. 14) 1926.

highest specific gravity, 1.032, was registered with a viscosity of 8; on the other hand, an effusion with a specific gravity of 1.019 had a viscosity of 43.

The concentration of the proteins that determines the specific gravity is, therefore, not the underlying cause of the variation in viscosity and the striking precipitation phenomena (sack formation). A review of the data published on the protein content of synovial fluids shows that it ranges between 0.5 per cent (Horyi¹²) and 7.25 per cent (Cajori and his associates⁶). If only the pathologic local effusions of the joints are considered, the range narrows from 3.5 to 7.25 per cent (Allison and his associates¹⁷), a difference of not more than 100 per cent, and is within the values for exudates and plasma.

The Diffusible Constituents.—Nonprotein nitrogen was found in equal concentration in plasma and synovial fluids by Fremont-Smith,¹⁸ Allison¹⁷ and Cajori⁶ and their co-workers. Cajori found also the amino-acids, urea nitrogen and carbon dioxide in synovial fluid to be in close approximation to the values for plasma.

Of the inorganic salts, calcium was found to vary from 4.6 to 9.4 mg. per hundred cubic centimeters in the material of Horyi, but no relation existed between the concentration of the calcium and protein and the specific gravity. Lesser variations from 8.3 to 10.7 mg. were reported in three cases by Cajori and his co-workers. In six fluids from patients with chronic nonspecific arthritis I found a range in calcium from 7.8 to 10.6 mg. per hundred cubic centimeters.

Salkowski first recorded the high content of 772 mg. of sodium chloride in his case. In comparative studies of joint fluids and plasma, Fremont-Smith, Allison and Cajori and their associates demonstrated the sodium chloride content to be higher in the former. The maximum difference of 54 mg. was found in Cajori and Pemberton's case 8, the sodium chloride in the plasma being 549 as opposed to 604 mg. per hundred cubic centimeters in the synovial fluid. In two patients of my series during a period of fasting, the chlorides were estimated in plasma and synovial fluids. The first had chronic synovitis which had developed after trauma to the right knee. Chlorides in the plasma amounted to 447 mg., and in the synovial fluid, to 562 mg. (a difference of 115 mg.). The second patient had hypertrophic arthritis with free bodies in the right knee; the amount of chlorides in the plasma was 472 mg., and in the fluid, 582 mg. (a difference of 110 mg.). Phos-

17. Allison, N.; Fremont-Smith, F.; Dailey, M. E., and Kennard, M.: Comparative Studies Between Synovial Fluid and Plasma, *J. Bone & Joint Surg.* 8: 758, 1926.

18. Fremont-Smith, F., and Dailey, M. E.: Studies in the Distribution of Chloride and Protein Between Plasma and Synovial Fluid, *J. Biol. Chem.* 70:779 1926.

phorus was estimated in the fluid from five patients with atrophic and hypertrophic arthritis. The values ranged between 3 and 3.9 mg. per hundred cubic centimeters. The sugar content of synovial fluids in non-infected cases was found by Fremont-Smith, Allison and their associates to vary between 58 and 119 mg. per hundred cubic centimeters. In ten fasting patients, the average value of sugar was 96 mg. in plasma and 84 mg. in synovial fluid, a difference of about 13 per cent. In fifteen nonpurulent cases reported by Cajori and his co-workers, the concentration was between 68 and 132 mg. per hundred cubic centimeters; however, these patients were not fasting, and the authors demonstrated the rise in the concentration of sugar with the ingestion of food.

In two tuberculous effusions, Allison and his associates found values for sugar of 45 and 61 mg., and in four fluids positive for gonococci and streptococci, the sugar was between 19 and 43 mg. The authors

TABLE 12.—*Cell Count and Sugar Content*

No.	Diagnosis	Cells	Polymor- phonuclear Leukocytes, per cent	Sugar, Mg. per 100 Cc.	Comment
1	Synovitis, knee.....	27,800	74	67	Trauma two years previously
2	Gonorrheal polyarthritis.....	26,100	86	70	Acute
3	Syphilitic bilateral arthritis, knee	18,300	66	99	Acute; congenital syphilis
4	Chronic syphilitic arthritis, knee	5,450	5	130	
5	Atrophic polyarthritis.....	4,300	22	92	Subacute
6	Traumatic synovitis, knee.....	2,300	65	123	Erythrocytes, 3,300,000
7	Chronic atrophic polyarthritis...	1,800	46	105	
8	Chronic arthritis, knee.....	1,400	68	96	Nonspecific
9	Synovitis, knee.....	900	2	94	Blood sugar at fasting, 82
10	Hypertrophic arthritis, knee.....	700	3	81	Blood sugar at fasting, 71

concluded that very low values may be indicative of bacterial infection. However, Cajori and Pemberton reported a case of purulent synovial fluid of unknown etiology in which the sugar was almost absent (from 8 to 10 mg.), and in which repeated cultures and inoculation in animals gave negative results. The cell count amounted to 13,880, of which 97 per cent were polymorphonuclear leukocytes. They carried out a glycolysis experiment on this fluid and on the cell-free filtrate by adding 30 mg. of dextrose to each portion. After incubation for seventeen hours, the full fluid showed a decrease in the sugar content from 145 to 27 mg., while the centrifugated specimen showed a decrease only from 121 to 114 mg. per hundred cubic centimeters. The authors concluded that glycolysis is due to the action of the leukocytes, irrespective of bacterial infection.

Some support is given to this conclusion by ten effusions of specific and nonspecific origin (table 12). The total cell count seems to have less influence on the glycolysis than the number of leukocytes present. Number 4 with 5,450 cells but only a few leukocytes had 130 mg. of sugar, while number 8 with only 1,400 cells had 68 mg. of sugar per

hundred cubic centimeters. In this case, however, the polymorphonuclears amounted to 68 per-cent. Fluid from these patients was aspirated in the afternoon and evening, and, therefore, the influence of the intake of sugar must be considered. In two patients (9 and 10) with non-infectious chronic arthritis (one posttraumatic, the other hypertrophic), sugar was estimated in the synovial fluids and blood which were simultaneously aspirated before breakfast. The synovial fluids contained, respectively, 94 and 81 mg. of sugar per hundred cubic centimeters. The sugar in the plasma was 82 and 71 mg., respectively. It can be seen, therefore, that in the fasting state, the sugar in the synovial fluids exceeded the sugar in the plasma, both patients' total cell counts were low, and the polymorphonuclear leukocytes were only from 2 to 3 per cent. It can be concluded that accurate information is obtained only if the estimation for sugar is carried out simultaneously on the plasma and synovial fluid of the fasting patient. According to Fremont-Smith and his associates, lower values for protein and higher values for chloride are found in pleural, peritoneal and spinal fluids, as well as in synovial effusions, than in plasma; in fact, this is true of all body fluids that are produced by dialysis. On the basis of their calculations, these authors found that the Donnan membrane equilibrium applies to the distribution of protein and chloride between synovial fluid and plasma. They concluded that pathologic effusions into the joints are derived from plasma by dialysis rather than by secretion. This theory will be discussed later.

Important as the rôle of the diffusible constituents may otherwise be, it has no significance in an explanation of the variation in viscosity and sack formation in synovial fluids. This is realized when one figures in percentages rather than in milligrams.

The highest value of sugar encountered does not exceed 0.15 per cent; that of sodium chloride is less than 0.8 per cent. In these concentrations neither has an influence on viscosity. According to Heyder and Rohrer,¹⁹ a solution containing salts and urea in the concentration of the blood has a viscosity of only 1.018.

Carbon dioxide increases the viscosity of fluids. However, Cajori and his associates found in synovial fluid a carbon dioxide percentage by volume of from 43 to 61, which is under the low reading for venous blood plasma.

Increased acidity may be responsible for a raise in viscosity. In an excellent review of the data on synovial fluids, Forkner²⁰ tabulated the p_H values according to different authors. For nonpurulent, inflammatory and traumatic fluids, the range of p_H is from 6.91 to 8.4. The

19. Heyder and Rohrer: *Deutsches Arch. f. klin. Med.* **121**:221, 1916.

20. Forkner, C. E.: *The Synovial Fluid in Health and Disease with Special Reference to Arthritis*, J. Lab. & Clin. Med. **15**:1187, 1930.

extreme values were obtained in few cases. In seven purulent, septic cases registered by Boots and Cullen, Cajori and Pemberton and Habler, the p_H ranged from 6.19 to 7.24. Hammarsten, Mayeda and Horyi found the reaction in their cases to be alkaline.

In thirty fluids in my material, from patients with acute and chronic, nonspecific, gonorrheal and syphilitic arthritis, the reaction to litmus was alkaline. One fluid, from the knee of a child with acute purulent arthritis, caused by injury through the driving in of a nail, gave an acid reaction. *Staphylococcus aureus* was present in great numbers in the smears and was readily grown in the cultures. However, on the day following the operation the reaction had already changed to alkaline. The viscosity dropped from 16 to 6.

TABLE 13.—*Reactions of Mucin, Mucoïd and Nucleoproteins*

Substance	Origin	3 Per Cent Acetic Acid Precipitin	Reduction of Copper Sulphates	Phosphorus
Mucin.	Saliva	Heavy	Positive	Negative
Pseudomucin.	Ovarian cyst	Negative	Positive	Negative
Ovomucoid.	Egg white	Slight	Positive	Negative
Chondromucoid.	Cartilage	Positive	Positive	Negative
Synovia mucin (von Holst ²²) .	Synovial fluid	Positive	Positive	Negative
Synovin (Salkowski ¹⁵)	Synovial fluid	Positive	Negative	Negative
Nucleoprotein.	Nuclei cyto globin	Positive (soluble in excess)	Negative	Positive

TABLE 14.—*Specific Gravity of Full and Supernatant Synovial Fluid **

No.	Full	Supernatant	Expected Value
1.	1.022	1.018	1.016
2.	1.022	1.017	1.016
3	1.023	1.018	1.016
4	1.026	1.013	1.013

* The specific gravity of the acetic acid used for precipitation was 1.004.

Therefore, as first brought out by Boots and Cullen,²¹ an acid reaction is found only in purulent arthritis. The p_H of nonpurulent fluid is within the range or exceeds the values of normal plasma.

The review shows that neither the total percentage of protein nor any of the diffusible constituents can explain the differences in the viscosity and precipitation phenomena of synovial fluids. It is therefore necessary to consider the different fractions of the proteins separately.

Globulins.—That globulin increases viscosity more than does albumin was stated by Heyder and Rohrer and experimentally proved in the curves quoted by Hatschek. The globulin content estimated by Cajori

21. Boots, R. H., and Cullen, G. E.: The Hydrogen Ion Concentration of Joint Exudates in Rheumatic Fever and Other Forms of Arthritis, J. Exper. Med. 36:405, 1922.

and Pemberton in twelve fluids varied from 0.3 to 3.45 per cent. A case of anasarca had the minute amount of 0.025 per cent. With the exception of one case, the corresponding content in the plasma was found to be higher. The ratio of albumin to globulin was 2 in the fluids and 1.9 in the plasma. In other words, in this material globulins made a smaller percentage of the total proteins than they did in plasma, with one exception. They can therefore not be responsible for the higher viscosity of these fluids. However, in fluid from an acute case of gonorrheal polyarthritis, containing 10,200 cells with a protein content of 6.43 per cent, the globulins amounted to 4.18 per cent and the albumin only to 1.31 per cent. The ratio is 0.314. The albumin only makes up 31.4 per cent of the globulins. The viscosity in this case was 16.8 (table 15).

The influence of the globulins was therefore determined directly by comparing the viscosity of the full fluids and a fraction freed from globulin by precipitation with equal parts of saturated ammonium sul-

TABLE 15.—*Protein Fractions in Synovial Fluid in a Case of Acute Gonorrheal Arthritis*

	Fraction	Synovial Fluid	
		Full, per Cent	Supernatant, per Cent
Protein		6.43	5.49
Albumin		1.31	.
Globulin		4.18	3.97
Mucin, calculated		0.94	.
Albumin globulin		0.314	...

phate. After centrifugation the clear supernatant fluid was pipetted off and the viscosity determined. Since the difference between the viscosity of water and that of the saturated ammonium sulphate was 1.4, half of this number (0.7) was subtracted from the viscosity of the globulin-free fraction and the rest multiplied by 2. The last column of number 1 in table 17 shows the decrease in the cited case to be 40.5 per cent. In five other determinations from cases of chronic infectious and noninfectious arthritis, decreases of viscosity between 11.8 and 42.5 per cent are registered. Although this appears to be a considerable percentage, the resulting viscosities still exceed the range for plasma and exudates, with the exception of one case of chronic prepatellar bursitis in which the full fluid has a viscosity of only 2.5 (no. 7 table 17).

The globulins, therefore, have a marked but only a limited influence on the viscosity of synovial effusions.

Fibrinogen.—That the content of fibrin varies in different fluids is demonstrated by the fact that some fluids coagulate completely within a short time after withdrawal; others show only fine threads of fibrin, and a great number remain liquid and clear on standing.

I found that fluids from patients with acute infections coagulated completely and quickly. However, quantitative estimations are needed to draw conclusions that may be of clinical value. As the viscosity is determined after the removal of clots, this variation of fibrinogen in the full fluid is immaterial. An estimate of the fibrinogen in the clear fluid has been attempted in fourteen cases of inflammatory and in eight cases of traumatic effusions by precipitation with equal parts of concentrated sodium chloride solution and incubation in the thermostat.

In the effusions of six cases of traumatic origin and eight cases of inflammatory origin only traces of fibrinogen were found. In two traumatic and six inflammatory effusions very thin floccules appeared, such as those seen in the control made with serum. Fibrinogen therefore was absent or present only in minute quantities in the clear fluids and had no influence on the viscosity.

The result of the investigation reveals that none of the colloids or diffusible constituents of plasma produce the high values, the wide range of viscosity and the precipitation phenomena found in fluids from normal and pathologic joints.

Before considering a component of synovial fluid not found in plasma, the mucinous substance, I shall discuss the relation of viscosity and specific gravity to the sack formation. High viscosity and specific gravity are not essential to such formation. Filtered saliva of a viscosity of only 1.6 shows this phenomenon. In synovial fluids, sack formation occurred at a viscosity of around 3 and at the lowest specific gravity (1.015). Viscosity and specific gravity determine the appearance of the sack. The sacks in saliva and in the fluids of low viscosity are thin and of short duration, while fluids of high viscosity produce sacks with thick membranes which are preserved indefinitely. At low specific gravity the sacks remain on the surface; at higher gravities the tube formation appears and the sacks sink to the bottom. The preservation of the sack depends on the resistance of the membrane and the gravity.

4. THE MUCINOUS SUBSTANCE

In 1846, Frerichs⁸ expressed the opinion that the difference in the appearance between transudates and synovial fluid is due to a mucinous substance that can be precipitated by acetic acid. He regarded the synovial membrane as an epithelium, the superficial cells of which undergo disintegration analogous to that of the horny layers of epidermis and form the mucons substance by dissolution in serum.

In 1882, Hammersten¹⁴ examined the mucin in two inflammatory effusions. They contained phosphorus. Therefore, he considered the substance as a nucleo-albumin. Salkowski,¹⁵ in 1893, carefully studied the chemical composition of the synovial fluid in a case of chronic coxitis. The mucinous substance was isolated by precipitation with acetic

acid, redissolution in sodium hydroxide, reprecipitation and repeated washing with alcohol and ether and finally dried in a desiccator over sulphuric acid. The substance amounted to 0.375 per cent. It did not contain phosphorus; after hydrolyzation by boiling with a weak solution of hydrochloric acid for from one to several hours, it did not reduce Trommer's sugar reagent. The absence of phosphorus proved the substance to be different from a nucleoprotein.

A calculation of the figures given by Hammarsten showed that the phosphorus content in the two fluids was only about 0.2 per cent. Nucleo-albumin of such low phosphorus content was not known, and Salkowski concluded that Hammarsten worked with a mixture of mucin and nucleo-albumin derived from the lymphocytes, which were present in these fluids in large numbers.

The absence of a compound nitrogenous sugar was proved by the negative outcome of the Trommer reaction. The mucins being glycoproteins which reduce copper sulphate readily, Salkowski regarded this substance as a special modification of mucin, which he called "synovin."

Von Holst²² isolated mucin from the synovial fluid of cattle by precipitation with diluted acetic acid in a similar procedure. Examination of the dry product was negative for phosphorus and on hydrolyzation reduced copper salts, thus giving all the reactions of a typical mucin. He made the observation that the supernatant fluid, after precipitation of the mucin, lost its viscous character.

The results obtained by both authors have established in the normal synovial fluids of cattle and the pathologic effusions of man the presence of a mucinous body that is free from phosphorus and therefore not derived from nucleoprotein or cytoglobulin. However, the effusion from a patient with coxitis did not give a positive sugar reaction.

These are the only complete analyses of the mucinous substance in synovial fluid that have been published. This substance was not considered again until 1923 and then in a brief statement by Fisher²³ that the mucin content was 1.95 per cent in normal synovial fluids secured at autopsy on man, and only 0.1303 per cent in oxen. No mention is made of the methods of preparation or analysis, the phosphorus content or the sugar reaction.

The last reference to mucin is found in the article by Cajori and Pemberton.⁶ They precipitated the mucin with acetic acid, in the manner of von Holst, removed the supernatant fluid by filtration and determined the nitrogen content either directly or by the loss of nitrogen in an aliquot part of the supernatant fluid. On the basis of von Holst's

22. von Holst, G.: Serosa Mucin; eine Mucinsubstanz im Ascites, Flüssigkeit und Synovia, Ztschr. f. phys. Chem. 43:145, 1904-1905.

23. Fisher, A. G. T.: Physiological Principles Underlying the Treatment of Injuries and Diseases of the Articulations, Lancet 2:54, 1923.

determination that the nitrogen content in the mucin is equal to 13.26 per cent, they estimated the quantity of mucin by multiplying the nitrogen with 7.54. No evidence was given that the elementary analysis found in the effusions of normal cattle applies to the normal and especially to the pathologic effusions in human beings. The procedure therefore cannot be accurate. No determinations of phosphorus or sugar reaction were carried out. However, the authors made the valuable observation that the viscosity of three fluids after precipitation of the mucin dropped to the level found in plasma.

My review has shown that the mucinous substance was prepared in dry form and thoroughly investigated in only one effusion. This analysis disagreed with an older as well as with a later analysis of the normal synovial fluid in cattle in two important points: phosphorus content and sugar reaction. A reinvestigation was therefore indicated.

By separating the precipitate from the supernatant fluid by centrifugation instead of filtration, the whole process was carried out in one test tube. This had the further advantage that fat, lutein and cholesterol were separated as a scum on the top of the tube, thereby saving separate extraction and loss of material. With this modification enough dry substance for complete analysis can be obtained from 30 cc. of fluid.

The mucinous substance was prepared in dry form in eleven fluids of traumatic, of acute and chronic synovitis and of nonspecific, syphilitic and gonorrheal arthritis.

Method of Preparation of the Mucinous Substance.—Centrifugate the synovial fluid until it is perfectly clear. Make sure, under the microscope, that no cells are present. Transfer the clear synovial fluid to large centrifuge tubes with wide bottoms. Add slowly half the amount of 3 per cent acetic acid. Shake and centrifugate for ten minutes. Remove the scum on the surface with a glass rod and decant the supernatant fluid. Fill to the original amount with 0.1 per cent sodium hydroxide. After dissolution, reprecipitate with half the amount of 3 per cent acetic and centrifugate. Decant the supernatant fluid, and wash the precipitate first with alcohol and then with water. Dry in a desiccator over sulphuric acid.

Traumatic effusions contain considerable bilirubin which is precipitated by the acetic acid. It is therefore necessary after the solution of the precipitate by the weak alkaline to add an equal volume of absolute alcohol and acidify by adding a few drops of glacial acetic acid and to centrifugate. The bilirubin is kept in solution by the alcohol. The supernatant fluid is yellow, and the precipitate turns whitish.

Properties of Mucinous Substance.—The mucinous substance is a yellowish or whitish amorphous substance with a waxy shine to the surface. It is translucent in thin plates, hard and nonflexible (fig. 5). It is soluble in diluted alkali, and the solution is sticky. It is insoluble in water, acids and alcohol. It can be precipitated by 3 per cent acetic acid, hydrochloric acid and alcohol. It does not contain phosphorus. Reduction of copper salts was negative. The reaction to the biuret test, modi-

fied according to my method,²⁴ was positive. Examination for purine bodies gave negative results. According to one estimation, it weighed 0.467 Gm. per hundred cubic centimeters of fluid.

Comment.—The reactions to acids and alkalines are typical for mucin. The absence of phosphorus and purine bodies excludes nucleoproteins (table 13). The sugar reactions were negative after prolonged hydrolyzation. Whether this is due to the absence of a nitrogenous sugar in the molecule or to some peculiarity, I am not prepared to state. Technical reasons prevented an elementary analysis, in which the determination of the sulphur content, especially, could throw light on the composition.

However, it is evident that the substance is not derived from disintegration of cartilage, as chondromucin readily reduces copper salts (table 12). The changes that take place in the fluid after precipitation reveal the significance of the mucinous substance.



Fig. 5.—Several specimens of dry mucinous substance from synovial fluid.

The Supernatant Fluid.—The supernatant fluid is whitish or yellowish, the latter in traumatic effusions containing bilirubin. It is clear or, if the globulin content is high, somewhat turbid. The specific gravity is only slightly lower than it is in full fluid. The calculation shows this to be caused by the addition of the lighter acetic acid (table 14). This indicates that no marked changes in the protein content or salts have taken place by the removal of the mucinous substances. This is confirmed by the direct estimation of protein and globulins in one case (table 15). In two cases (table 16), the diffusible contents of blood, full and supernatant fluid are compared. If allowance is made for the limit of error, the differences are insignificant. The supernatant fluid still contains the bulk of colloids and diffusible constituents.

An enormous drop, however, occurred in viscosity equal to a decrease between 312 and 1,780 per cent (table 17). The range of variation between the minimum of 0.8 and the maximum of 1.09 is well within the limits of viscosity for transudates and exudates. The peculiar

24. Kling, D. H.: A Convenient Modification of the Biuret Test. *J. Lab. & Clin. Med.* **15**:185, 1929.

precipitation phenomena disappeared. The fluid no longer showed sack formation but gave either a positive or a negative Rivalta reaction. In short, the supernatant fluid has all the physical and chemical characteristics of simple transudates or exudates.

TABLE 16.—*Chemical Analysis of the Blood and of Full and Supernatant Synovial Fluids in a Fasting Patient, Expressed in Milligrams per Hundred Cubic Centimeters*

Fluid	Sugar	Urea Nitrogen	Creatinine	Chlorides	Calcium*	Phosphorus*
Blood.....	82	11.3	1.77	477	10.1	3.12
Synovial.....	94	12.1	1.50	562	7.8	2.96
Supernatant.....	94	13.1	1.39	600	8.8	2.84

* Estimated on a second fasting patient.

TABLE 17.—*Specific Viscosity of Synovial Fluid Determined in Full, Supernatant and Globulin-Free Specimens*

No.	Specific Viscosity				
	Full	Supernatant (Mucin-Free)	Decrease, per Cent	Globulin-Free	Decrease, per Cent
1.....	16.8	1.6	1.050	10.0	40.5
2.....	10.0	0.9	1.718	9.6	40.0
3.....	10.0	0.9	1.718	0.2	42.5
4.....	32.0	1.9	1.780	28.2	11.8
5.....	13.6	1.9	0.720	9.2	32.3
6.....	13.4	1.4	0.960	9.2	31.3
7.....	2.5	0.8	0.312	1.6	36.0
8.....	23.0	1.8	1.550
9.....	16.8	1.6	1.050
10.....	16.0	1.6	1.000
11.....	11.4	1.7	0.670
12.....	12.0	1.3	0.920
13.....	14.8	1.2	1.220

TABLE 18.—*The Composition of Synovial Fluids*

Origin	Synovial Membrane	Circulation	
Supplies.....	Mucinous substance	Plasma	
Properties.....	Synovial cells	Blood cells	
	Protection, lubrication	Nutrition	
	Antibodies	Antibodies	
Composition of Special Types			
Type	Source	Cells	Percentage*
Normal fluid.....	Synovial membrane	Tissue	
Transudates.....	Circulation	None	2
Exudates.....	Circulation	Blood	4
Inflammatory and traumatic effusions	Circulation and synovial membrane	Blood and synovial cells	94

* Calculated on the basis of 200 pathologic effusions.

A direct proof that the mucinous substance produces both the precipitation reactions and the increase in viscosity is given in the following experiment. About 5 mg. of the dry substance was dissolved in 10 cc. of serum to which a drop of 10 per cent sodium hydroxide was added. The viscosity of the serum was raised from 1.7 to 4, and sack formation appeared. Previously even the Rivalta reaction had been negative.

THE ORIGIN OF NORMAL AND PATHOLOGIC SYNOVIAL FLUIDS

This investigation revealed a dual composition of pathologic effusions. The supernatant fluid after precipitation with acetic acid contains proteins and diffusible constituents of plasma, transudates and exudates. Their distribution indicates that they are derived from the circulation by diffusion (Fremont-Smith). They represent the systemic response to inflammation. In traumatic effusions they are carried into the joint cavity by the rupture of a vessel. The mucin-like precipitate, however, is not present in the plasma. It is produced by the synovial membrane. It is demonstrated in the fluids of normal joints as well, and must therefore be regarded as a physiologic product. Inflammation and irritation only tend to increase its output. This substance determines the physico-chemical properties of synovial fluid, like stickiness, sack formation, viscosity and precipitation. Its biologic function is entirely different from the fraction derived from the circulation. The proteins and crystalloids of the latter are a source of energy and nutrition. The mucinous substance is adopted for protection and lubrication of the articular surfaces.

This is a foremost requirement of the working, healthy joint. Normal synovial fluid consists, therefore, of a small amount of this colloidal lubricant furnished by the membrane according to the requirement for proper function. The fine adjustment that characterizes living matter is well demonstrated in the synovial fluid.

The slightest disturbances, like the absence of motion (Frerichs and Horyi), are of influence. Irritation and inflammation produce changes in the amount and composition of synovial fluid proportional to the degree of disturbance. This applies to the cellular elements as well as to the liquid portion.

Normal synovial fluid contains few cells, and they are chiefly synovial lining cells.²⁵ Different types of leukocytes in various amounts, according to the stage and the degree of the process, are found in inflammatory effusions; trauma brings red blood corpuscles into the fluid.

The Mechanism and the Place of the Elaboration of Normal Synovial Fluid.—Changes in anatomic conceptions of the synovial membrane resulted in different theories regarding the source of synovial fluid. Some still propose that it is a product of disintegration either from the superficial cells of the synovia (Frerichs) or from cartilage (Ogston²⁶ and Bianchi²⁷). This is based on an erroneous analogy to the horny layers of epidermis.

25. Kling, D. H.: Synovial Cells in Joint Effusions, *J. Bone & Joint Surg.* 12:867, 1930.

26. Ogston, quoted by Fisher (footnote 23).

27. Bianchi, quoted by Mayeda (footnote 13).

The superficial lining cells of the synovia are seen to be intact in fresh preparations; their nuclei and cytoplasm stain well. Also the superficial cells of the articular cartilage appear healthy; they are nearest to the perichondrium in the lateral parts of the cartilage. Fisher advances the theory that the superficial cells generate the deeper layers in the central portion.

Benninghoff²⁸ demonstrated that their fibers form an important system in the architectonic structure of the articular cartilage. The clean appearance of the normal joint cavity and the small amount of débris in the contents also disprove this antiquated theory.

The conception of the synovial membrane as a modified connective tissue, not endowed with secretory elements, advanced the theory that the synovial fluid is a transudate. The analysis has demonstrated that this applies only to one fraction of the pathologic effusions. The physicochemical properties and the function indicate that the normal synovial fluid is a product of specialized cell activity.

The anatomic basis for this view was furnished by an extensive histologic study by Mayeda. The synovial membrane is not of uniform structure. In 1894, Hammer noticed the great variation in the forms and the number of the lining cells. Key²⁹ recently emphasized the variation in the subsynovial tissue.

Mayeda proved that the function of different parts varies with the structure. The distal part of the suprapatellar bursa and the membrane of the posterior aspect of the knee joint are composed of a firm connective tissue and covered by a single and partly interrupted row of small, flat cells. The plica adiposa, the fornix of the suprapatellar pouch and the villi contain loose subsynovial tissue and several rows of large polygonal cells. By special staining methods, Mayeda demonstrated in some of these cells Altmann granules, Haidenhain granules and also mucin granules. These gave a positive oxydase reaction, and accumulated and excreted colloidal iron solutions, injected intravenously. The secretory nature of the cells producing the mucinous substance was therefore proved.

Timbrell Fisher in a later publication observed mucin in cells of the villi, stained with thionine. In preparations fixed with sublimate and stained with toluidine blue, I have demonstrated in sections and in scrapings the presence of cells with metachromatic reddish or purple granules that filled the cytoplasm. The nuclei were normally shaped and well stained, and were therefore not degenerated.

28. Benninghoff, A.: Die modellierenden und form-erhaltenden Faktoren der Knorpelreliefs, *Ztschr. f. d. ges. Anat.* 76:43, 1925.

29. Key, Albert: *Synovial Membrane in Special Cytology*. New York, Paul B. Hoeber, Inc., 1928, vol. 2.

In summary it can be said that the structure and the function of the synovial membrane are twofold. One part is built for mechanical binding of the epiphyses constituting the joint; it is connective tissue capsule, inward and outward. The other part is interposed at the intra-articular surfaces, for the maintenance of smooth motion and lubrication. This is the function of the intra-articular fat depots, synovial folds and villi and their lining containing actively secreting cells.

The conception of the composition of the synovial fluid on the basis of these studies is summarized in table 18. Normal fluid is chiefly secreted by the synovial membrane. Transudates and exudates forming 6 per cent of a series of 200 fluids are derived from the circulation. Ninety-four per cent of the traumatic and inflammatory effusions contained products of both circulation and synovial secretion.

CLINICAL CONSIDERATIONS

The clinical significance of the differentiation of the structure of the membrane and of the normal and pathologic synovial fluids is a subject for separate study. Here I shall point out briefly some of the applications.

The Protective Influence of Synovial Secretion.—The development of the membrane and of the fluid is different in various joints. The secretory element is best developed in the knee joint and less well developed in the wrist and tarsal joints. The primary response to inflammation and irritation of the knee is therefore effusion; that of the wrist, infiltration and pannus formation. This explains why the same etiologic factor, for instance gonorrhea, produces in the same patient a chronic exudative arthritis of the knee joint and an infiltrative and ankylosing process of the wrist.

Motion is the natural stimulus for the secretion of synovia, as is food for the secretion of gastric juices. The detrimental effect of immobilization, especially in knee joints, is therefore explained by the interference with this secretion in a joint highly adapted to it.

The protective action of the synovial secretion is further seen by the fact that forms of arthritis with effusions generally have a better prognosis than the infiltrative, atrophic forms. In the latter the synovial membrane undergoes early destruction, and the process spreads over the cartilaginous and bony surface without a barrier. The atrophy reaches a high degree and ankylosis occurs. In arthritis with effusions, inflammation is met with hypertrophy and hypersecretion of the membrane, the articular surfaces are protected, and the resulting atrophy is only proportional to the decrease in function.

The Relation Between Trauma and Inflammation.—Physiochemical analysis has demonstrated the almost immediate reaction of the synovial

membrane to intra-articular injuries. Of the seventy-eight cases of acute hemorrhagic effusion, only two contained blood corpuscles and serum alone. The hemorrhagic fluid in all others had a high viscosity, sack formation occurred, and the mucinous body was precipitated by acetic acid, even in the first days after injury. Besides the mechanical disturbance, the hemarthrosis therefore produces an irritation and hypersecretion. Although self-limited by absorption in the majority of injuries, in some cases the process continues. This explains the frequent transition of traumatic effusion into chronic synovitis and the development of diminished resistance in injured joints. In many cases of monarticular arthritis, careful inquiry reveals a trauma preceding by months and even years an inflammatory process, which may have been brought about by influenza, tuberculosis, syphilis or gonorrhea.

Osteochondritis Dissecans and Loose Bodies.—Osteochondritis dissecans and loose bodies offer a good opportunity to demonstrate the difference in function of the two components of synovial effusions. The pathologic process in osteochondritis dissecans consists of the necrosis of a shell of the articular cartilage. If Strangeways' ³⁰ and Fisher's contentions that normal synovial fluid has a nutritive value are true, how could the necrosis ever have taken place? Even if the shell were cut off from the circulation, it could find nourishment in the synovial fluid. This is not the case as long as the necrotic piece of cartilage is still attached. In my cases, I had the opportunity to observe at operation that no irritation of the synovial membrane was present; the synovial fluid was normal in amount and composition. As soon, however, as the fragment of cartilage becomes detached and free it impinges on different parts of the membrane during motion and produces irritation and transudation from the vessels, which import the proteins and sugar needed for nutrition by diffusion.

The cartilage cells start to generate and the loose bodies grow. Unlike necrosis without detachment, effusion is usually associated with loose bodies. They grow, therefore, because they produce their pabulum and not because it is already formed.

SUMMARY

Studies on the source and origin of synovial fluid were carried out on a material of thirteen normal fluids and two hundred pathologic effusions.

Normal fluids and about 95 per cent of the effusions gave precipitation phenomena with diluted acetic and hydrochloric acid, consisting of

30. Strangeways, T. S. P.: The Nutrition of Articular Cartilage, Brit. M. J 1:661, 1920.

membranes and sacks. Analogous phenomena were found with mercuric chloride solution, and somewhat modified phenomena with alcohol.

These reactions were not found in plasma transudates and exudates from other cavities of the body; they were, however, demonstrated in fluids that were cell secretions, like saliva and egg white.

The viscosity of normal, and the majority of pathologic, synovial fluids is higher and the range of variation is greater than that found in plasma and exudates.

The specific gravity, on the other hand, is in the range of that for body fluids.

Accordingly, the substances that determine the specific gravity, the proteins and crystalloids and their fractions, were found to be in the range of these fluids.

It was experimentally proved that none of the colloids and diffusible constituents of plasma produce a difference in viscosity and formation of sacks. The blood gases and the p_{H} were demonstrated to be without marked influence.

A mucinous substance was prepared in dry form from the effusions of the joints, which was proved to be responsible for the physicochemical properties of synovial fluids.

Mucin granules were demonstrated by special staining reactions in active cells in well defined areas of the synovial membrane, confirming the earlier work of Mayeda and of Fisher.

The mucinous substance is recognized to be a physiologic product.

Motion is the adequate stimulus, and lubrication and protection are the functions, of this secretion.

Normal synovial fluid is finely adjusted to the physiologic requirements.

Mechanical or inflammatory disturbance of the structure and function of the joint causes changes in the amount and composition of this secretion.

Ninety-four per cent of the pathologic effusions in this material were derived from both cell secretion and circulatory extravasation.

Four per cent are considered to be pure exudates or transudates.

On the basis of the physiochemical and anatomic studies, the view is advanced that the structure and function of the synovial membrane are twofold: a connective capsule for binding purposes in which secretory elements are interposed.

The clinical applications of these studies are illustrated in a number of pathologic conditions.

The material for these studies was derived from the orthopedic services of Drs. Harry Finkelstein, Henry C. Frauenthal, Samuel Kleinberg and Leo Mayer of the Hospital for Joint Diseases.

THE UNION OF GRAFTS OF LIVE AND OF PRESERVED FASCIA WITH MUSCLE

A COMPARATIVE STUDY *

S. L. HAAS, M.D.

SAN FRANCISCO

The study of the union of normal fascia with muscle has been the subject of a number of investigations. Because of the close relationship of this problem to the one to be presented it seems advisable to review some of these papers briefly.

In a report based on experimental and clinical observations, Seelig and Chouke¹ stated that muscle would not unite with fascia. They performed a series of experiments on animals, in which they reduplicated the fascia lata to simulate Poupart's ligament, and sutured the edge of the turned flap to the underlying muscle. In every experiment they found that the fascia lata was separated from the muscle by loose areolar tissue and failed to unite firmly. Koontz² repeated the experiment of Seelig and Chouke, but removed the loose areolar tissue from the fascia lata; he obtained firm union in every case. He claimed that the failure of the other investigators was due to the fact that they did not remove the fat. Seelig and Chouke³ each independently repeated their experiments, removing the adipose tissue, and again found that the fascia failed to unite. Rosenblatt and Cooksey,⁴ in a similar series of experiments, obtained union in every instance. Hertzler⁵ thought that the discrepancies in the results of the various investigators was due to the fact that Seelig and Chouke tied their sutures loosely and thus did not produce the traumatic reaction that is fundamental in obtaining a firm union. The other investigators tied their sutures tightly, and so caused the fibrous stimulation that is necessary for union in the presence of fat.

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* From the Surgical Laboratory, Stanford Medical School.

1. Seelig, M. G., and Chouke, K. S.: A Fundamental Factor in the Recurrence of Inguinal Hernia, *Arch. Surg.* **7**:553 (Nov.) 1923.

2. Koontz, A. R.: Muscle and Fascia Suture with Relation to Hernia Repair, *Surg. Gynec. & Obst.* **42**:222 (Feb.) 1926.

3. Seelig, M. G., and Chouke, K. S.: Fundamental Principles Underlying the Operative Cure of Inguinal Hernia, *J. A. M. A.* **88**:529 (Feb. 19) 1927.

4. Rosenblatt, M. S., and Cooksey, W. B.: Muscle Fascia Suture in Hernia, *Ann. Surg.* **86**:71, 1927.

5. Hertzler, A.: Healing of Muscle to Fibrous Tissue, *J. A. M. A.* **88**:1098 (April 2) 1927.

The preponderance of evidence from all of these studies favors the view that muscle will unite with fascia.

The next problem to present itself was whether or not a transplant of free fascia would unite with muscle. Some surgeons, particularly Lange, have held that transplanted fascia would not unite firmly with muscle fibers. These assertions were made in spite of the fact that Payr, in 1913, had successfully used transplanted fascia lata for the union of the cut end of the trapezius muscle to the tendon of the long heads of the biceps. Gallie⁶ likewise used a transplant of free fascia interwoven into the trapezius muscle and then united it to the humerus to replace a paralyzed deltoid. Mayer's⁷ operation, based on a principle similar to that of Gallie, but with a somewhat different mechanical arrangement, *also depends on the union of transplanted fascia to muscle.*

In addition to the successful clinical results just reported, I performed a series of experiments⁸ in order to determine the details of the union of live fascia with muscle. As the results of these experiments are to be compared with those of the present investigations, a review of that paper will be helpful in formulating the conclusions of the two.

The study consisted of six experiments performed on dogs in which a piece of fascia lata was removed from the outer side of the thigh and sutured to the cut end of one of the hamstring muscles with silk. As early as sixteen days after the operation, the transplanted fascia was found to be firmly united to the cut end of the muscle. The union became firmer with the lapse of time, and at eighty days the transplanted fascia took on a tendinous structure. Microscopic examination showed that the endomysium and perimysium of the muscle played the major rôle in forming the union with the fascia. The muscle cells appeared to have taken an active part in the uniting process. The muscle cells became transformed into elements of fibrous tissue which intermingled with the transplanted fascia. There was also evidence that the connective tissue fibers of transplanted fascia took an active part in the union.

These experimental observations and the clinical results established the fact that live, transplanted fascia will unite with muscle. No exact experimental work or clinical results have thus far been presented to show whether dead transplanted fascia will unite with muscle. If fascia

6. Gallie, W. E., and Le Mesurier, A. B.: The Use of Living Sutures in Operative Surgery, *Canad. M. A. J.* **11**:504, 1921.

7. Mayer, L.: Transplantation of the Trapezius for Paralysis of the Abductors of the Arm, *J. Bone & Joint Surg.* **9**:412 (July) 1927.

8. Haas, S. L.: Free Fascial Grafts; Their Union with Muscle, *California & West. Med.* **32**:387 (June) 1930.

is an inert tissue, as claimed by Nageotte,⁹ one would infer that dead tissue could be utilized just as successfully as live tissue for purposes of transplantation. On the other hand, if the cellular elements of transplanted live fascia play an active part in the union, and there is evidence that they do, it may be advantageous to utilize live tissue instead of preserved fascia. Furthermore, the chemical fixation of the tissue may hinder the union.

Koontz¹⁰ used preserved fascia for suture material in the repair of hernia. Although his experiments are not exactly comparable to the union of muscle and preserved fascia, they are of sufficient interest to warrant reporting at this time. He found that if fascia that had been preserved in alcohol, was transplanted into a defect in living fascia, it intermingled so closely with the live tissue that it was almost impossible to distinguish the dead from the living part. Heterografts were just as successful as homografts. Following the method of Gallie and Le Mesurier, Koontz then successfully utilized sutures of preserved fascia lata from the ox to unite the tissues in hernia in man. Rosenblatt and Meyers¹¹ performed a series of experiments in which they sutured the edge of the rectus muscle to Poupart's ligament with preserved ox fascia and tendon sutures. In studying the completely healed line of suture, they found that the preserved fascia sutures were smaller than they had been when they were inserted, and that there was some evidence of foreign body reaction. Koontz and Nageotte did not report the presence of foreign body giant cells or evidence of absorption in their experiments.

The direct union of a preserved piece of fascia with muscle presents a more complicated problem than the utilization of fascia for suture material. In the following set of experiments the problem is directly attacked and it is hoped that some light may be thrown on this interesting subject.

REPORT OF EXPERIMENTS

Seven experiments were performed on dogs under general ether anesthesia. The fascia lata was obtained prior to the operation and preserved in alcohol. At the time of the operation it was washed in sterile water. It was thought that the staining of the tissue with methylene blue (methylthionine chloride, U. S. P.) or gentian violet would tend to differentiate it on gross examination, but the stain disappeared by the time the animal was killed. In all of the experiments an incision was made on the inner posterior side of the hind leg, one of the hamstring muscles being exposed. A piece of tendon and muscle was removed and a seg-

9. Nageotte, J., and Sencert, L., quoted by Koontz, A. R.: *Ann. Surg.* **83**: 523, 1926.

10. Koontz, A. R.: *Experimental Results in the Use of Dead Fascia Grafts for Hernia Repair*, *Ann. Surg.* **83**:523, 1926.

11. Rosenblatt, M. S., and Meyers, M.: *Muscle-Fascia Suture with Preserved Fascia and Tendon*, *Surg. Gynec. & Obst.* **47**:836, 1928.

ment of preserved fascia sutured into the defect. At the end of the period of observation the animals were killed by an anesthetic, and the specimen was removed and studied grossly and microscopically.

EXPERIMENT 1 (dog DT3).—An incision was made on the inner side of the left leg just above the knee joint, exposing the semimembranosus muscle. A section of the muscle, including a part of the tendon, was removed and a piece of the preserved fascia lata was sutured into the gap with silk sutures. The wound was closed in layers, and the animal allowed its freedom.

When the dog was killed at the end of twenty-two days, the transplanted fascia was found to have firmly united to both the muscle and the tendon (fig. 1). The fascia was a mottled yellowish white, differing from the uniform grayish white of the live, transplanted fascia.



Fig. 1 (experiment 1).—Gross appearance of the union of dead fascia with muscle. The smaller photograph is a longitudinal section through the fixed specimen. It shows the close intermingling of the muscle and the fascia.



Fig. 2 (experiment 2).—Gross appearance of the union of dead fascia with muscle.

Microscopic examination showed that there was a close intermingling of muscle and fascia at the site of union. The endolysium (fascia uniting the individual muscle cells) and the perimysium (fascia uniting the bundle of muscle cells) were the most active elements in the uniting process. At the end of the muscle cells there were clumps of nuclei which were not giant cells but which appeared to be formed by an active proliferation of endomysium and nuclei of the muscle cells. Some of the nuclei were undergoing indirect division. The fibrillae of the muscle cells were breaking down and appeared to be engaging in the process of union. One could not distinguish between the dead, preserved tissue and the live tissue. It is to be remembered that the preserved tissue had been fixed in alcohol, and that which had not been replaced by ingrowing tissue had, owing to its fixation, retained the property of taking the usual stains.

EXPERIMENT 2 (Dog DT3).—The semimembranosus muscle was exposed on the right side and a piece excised from the muscle at its transition into the tendinous portion. A segment of preserved fascia was sutured into the gap.

Gross examination after thirty-eight days showed that the preserved fascia that had been stained in gentian violet before its implantation was completely decolorized (fig. 2). The union was firm, but the healing was not so uniform as when a live piece of fascia was utilized. Microscopic examination revealed a gradual transition from the muscle to the transplant of preserved fascia. The elements



Fig. 3 (experiment 2).—Photomicrograph showing the breaking down of the muscle cells. The fibrillae of these cells take on a wavy, fibrous, tissue-like structure and invade the transplanted preserved fascia.

of muscle were undergoing fragmentation. The fibrillae of the muscle cells had taken on a wavy structure (fig. 3) and gradually merged into the fibrous tissue structure of the transplanted fascia, no line of demarcation being made out. The transplanted fascia was more cellular than normal, which must have been due to additional, new elements of invading tissue from the muscle.

EXPERIMENT 3 (Dog DT3).—The semimembranosus muscle on the left was exposed, and a segment of muscle and tendon removed at the junction of the

muscle with the tendon. A piece of preserved fascia was sutured to the muscle in such a manner that the fascia was within the outer layers of muscle.

After forty-two days, examination of the gross specimen showed that the fascia was firmly united to the muscle. Its consistency was fairly firm, but it appeared to have lost some of its elasticity. The union with the tendon was likewise quite firm. Microscopic examination revealed that the process of union was more advanced than had been found in the earlier stages. The two tissues graded off so uniformly that there was no line of demarcation to distinguish the site of union (fig. 4).

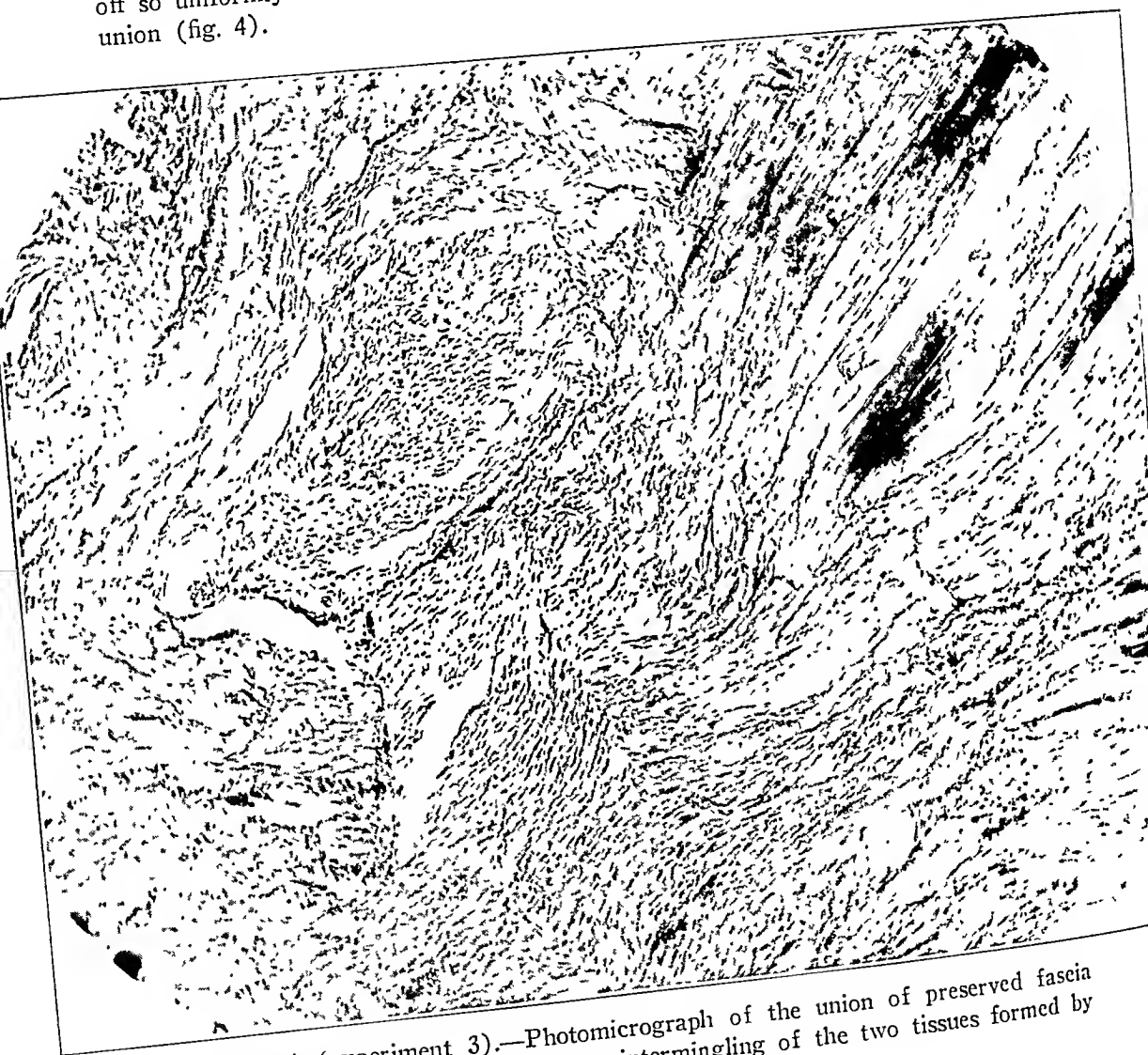


Fig. 4 (experiment 3).—Photomicrograph of the union of preserved fascia with muscle. This shows the close intermingling of the two tissues formed by the endomysium, perimysium and muscle cells.

EXPERIMENT 4 (Dog DT4).—The semimembranosus muscle was exposed on the left, and a piece removed at the place where the muscle passed into the tendon. A segment of preserved fascia lata was sutured into this defect with interrupted silk sutures.

In spite of an infection that had taken place, examination of the gross specimen after forty-two days showed that there was firm union between the fascia and the

muscle. The transplanted fascia and surrounding tissues appeared edematous. Microscopic examination showed a definite union between the muscle and fascia. The endomysium and perimysium were invading the transplanted fascia. The muscle cells themselves appeared to be taking part in the union.

EXPERIMENT 5 (Dog DT1).—The semimembranosus muscle was exposed on the left side by an incision on the inner side of the leg above the knee joint. A section of muscle and tendon was excised where the muscle passed into the tendon. Into this gap a piece of preserved fascia lata was sutured so that the fascia extended around the cut end of the muscle.

After forty-three days, examination of the gross specimen showed that there was firm union between the muscle and the transplanted fascia. The fascia itself was firm and had taken on a tendinous structure. The union between fascia and tendon was also firm. Microscopic examination under low power magnification showed the junction of the muscle with the fascia. There was a lighter staining fibrous tissue near the muscle that merged into a darker, red-staining tissue. The lighter tissue probably represented the new fibrous tissue that formed the union of the two, while the darker staining tissue represented the dead (fixed) fascia that had not been changed. Under higher magnification, a proliferation of fibrous tissue from the muscle side could be seen. Undoubtedly, the greater part of this proliferation was from the perimysium and endomysium. A close study of the muscle cells showed what appeared to be a breaking up of the fibrillae and their change into fibrous tissue-like elements. In places there was a proliferation of the nuclei about the ends of the muscle, forming budlike masses. Thus it appears that union takes place through a proliferation of the perimysium and endomysium and to a lesser degree through the breaking down of muscle cells. That there may be an ingrowth of fibrous tissue from the outside cannot be ruled out, but one gets the impression from the general longitudinal architecture and lack of invading tissue that the elements of muscle alone are concerned in the union.

EXPERIMENT 6 (Dog DT1).—Through an incision on the inner side of the right leg just above the knee joint, the semimembranosus muscle was exposed, and a segment of muscle and tendon was removed at their junction. A piece of preserved fascia lata was inserted into the gap and held with interrupted silk sutures.

The dog was killed after sixty-three days, and examination of a gross specimen showed that the transplanted fascia was firmly united to the muscle. The whole transplant was gelatinous and edematous, and lacked the firm consistency found when live transplanted fascia was utilized. Microscopic examination showed a direct union of the muscle with the fascia. The cellular response did not appear to be as active as in the earlier stages. This may have been due to the fact that there was less demand in this particular case because of the close approximation of the two. The fibrillae of the muscle cells appeared to be breaking down, and there was an increase in the number of nuclei at their ends. Both the sarcolemma and the endomysium showed evidence of cellular activity.

EXPERIMENT 7 (Dog DT4).—An incision was made on the inner posterior side of the right knee joint, one of the hamstring muscles being exposed. A section of muscle was removed and a piece of preserved fascia lata sutured into the gap with interrupted silk sutures.

The animal was killed after sixty-three days, and examination of the gross specimen showed that the preserved fascia had united firmly to the muscle. In this experiment, the fascia had been placed in a gap in the muscle, the distal portion of which had degenerated and was replaced by fibrous tissue. Microscopic

examination showed that the muscle and preserved fascia were closely united. The endomysium and the perimysium supplied the greater part of the connective tissue to the union. The muscle cells appeared to be transforming into elements of fibrous tissue and sharing in the union.

SUMMARY

In all of the seven experiments, the transplanted, preserved fascia united firmly with the muscle. At the end of twenty-two days, which was the earliest observation, union was almost secure. With the elapse of further time the union was more complete. The transformed tissue did not tend to take a firm, tendinous structure, but in general was somewhat gelatinous (edematous). Pathologic examination showed

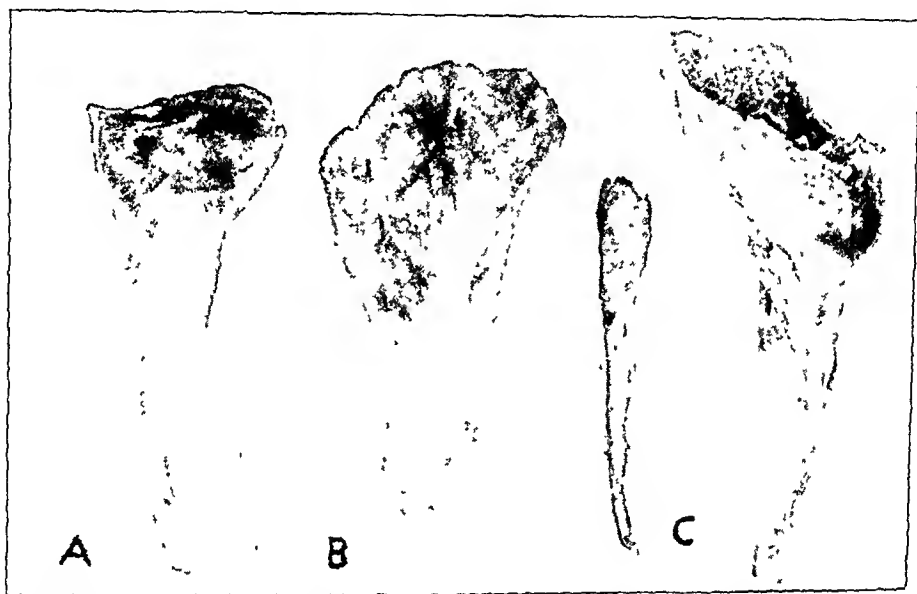


Fig. 5.—(A) Specimen showing the junction of normal muscle with tendon. (B) Section through the union of transplanted fascia with muscle. (C) Section through transplanted, preserved fascia with muscle.

a close intermingling of the muscle and the transplanted fascia. The endomysium and the perimysium played the major rôle in the union. The muscle cells showed definite evidence of proliferation and of having aided in the uniting process. There was no evidence of foreign body reaction or absorption, and the collection of nuclei in groups was interpreted as proliferating cells.

Comparison of Live and Preserved Fascia.—The union of the preserved fascia lata with the muscle apparently took place as rapidly as that with live fascia. The preserved fascia lata looked more edematous and appeared to be less compatible to the surrounding tissues (fig. 5). The live fascia was more tendinous and retained more of its elasticity.

On microscopic examination, there was no apparent difference between the union of dead fascia with muscle and that of live fascia (fig. 6). The same elements took part in the union, the greater amount coming from the endomysium and the perimysium, and there was the same evidence that the muscle cells shared in the process. Although grossly there was some sign of foreign body reaction when dead fascia was employed, no foreign giant body cells or evidence of absorption were

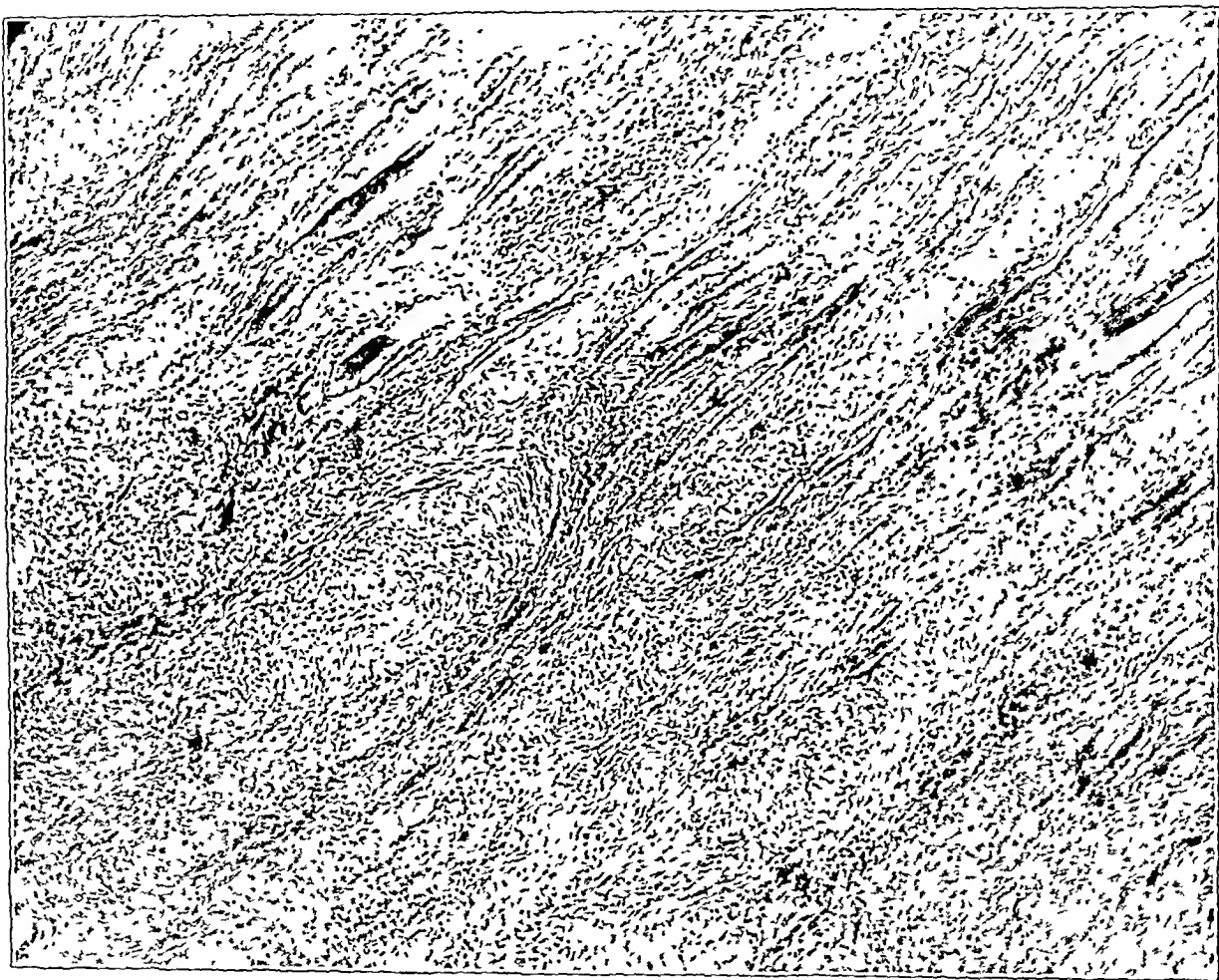


Fig. 6.—Photomicrograph of the junction of muscle with live, transplanted fascia. Notice the similar histologic picture to that found in the union of transplanted, preserved fascia with muscle in figure 4.

found in the dead fascia. One could not say whether the dead fascia survived permanently or was replaced by ingrowing tissue from the muscle, or that both shared in the process.

CONCLUSION

Dead, preserved fascia lata united with muscle just as rapidly and as firmly as did live fascia lata. The union of both dead and live

fascia depended mainly on the ingrowth of the endomysium and perimysium. The muscle cells themselves appeared to be transformed into elements of fibrous tissue and to aid in the uniting process. There was some evidence that the preserved fascia lost some of its elasticity and stirred up more reaction in the surrounding tissue than did live fascia. Dead, preserved fascia may be used clinically for union with a muscle, but it seems advisable to utilize the live fascia if possible, because the latter appears to be transformed into tendinous tissue more readily.

SKELETAL METASTASES ARISING FROM CARCINOMA AND FROM SARCOMA *

MURRAY M. COPELAND, M.D.

NEW YORK

Advances in the diagnosis and treatment of a disease entity are dependent on a knowledge of all the available data both from a clinical and from a pathologic point of view and from the results obtained by the various modes of therapy.

In the following study, an attempt will be made to correlate the various clinical features with the pathologic process involved, and to throw some light on the rather obscure results that have hitherto obtained in the treatment for metastases of the bone.

For purposes of analysis, it has been found convenient to group the 334 cases of bony metastases according to the primary tumor from which the dissemination occurred, thus emphasizing the entire clinical picture of each type of secondary neoplastic deposit, and, so far as possible, to determine accurately the process of histogenesis and the variations in response to treatment.

CARCINOMA OF THE BREAST

Carcinoma of the breast constitutes one of the most frequent primary tumors metastasizing to bone.¹ A survey of 1,914 cases of mammary carcinoma in the Surgical Pathological Laboratory of the Johns Hopkins Hospital revealed 903 deaths, 757 of which were caused by dissemination of cancer and 146 from causes other than malignant disease. In 89 (11.8 per cent) cases in which death was due to cancer, lesions of the bone were found prior to death. In addition to these fatal cases, 12 other patients, not yet reported dead, have developed metastatic

* Submitted for publication, Sept. 29, 1930.

* Illustrations by Herman Schapiro.

* From the Department of Surgery and the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

1. Joll, C. A.: Metastatic Tumors of Bone, *Brit. J. Surg.* **11**:38, 1923-1924. Moore, A. B.: A Roentgenological Study of Metastatic Malignancy of the Bones, *Am. J. Roentgenol.* **6**:589 (Dec.) 1919. Carnett, J. B., and Howell, J. C.: Bone Metastases in Cancer of the Breast, *Ann. Surg.* **91**:811 (June) 1930. Handley, W. S.: Cancer of the Breast and Its Operative Treatment, London, John Murray, 1906, pp. 1-176. Kaufmann, E.: Sekundäre Geschwülste der Knochen, *Spezielle pathologische Anatomie* **1**:954, 1922. Gross, S. W.: Skeletal Metastases in Carcinoma of the Breast, *Am. J. M. Sc.* **95**:219, 1888. Ginsburg, S.: Pain in Cancer of the Breast: Its Clinical Significance with Special Reference to Bone Metastases, *ibid.* **171**:520, 1926.

TABLE 1.—Cases of Carcinoma of the Breast with Metastases to Bone

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
44695	W	F	40	Cystic adenoma, carcinoma	Right breast	Gland biopsy, right axilla	5th, 6th and 7th thoracic vertebrae	27 months	3 months	Radium, 6 Gm. hrs.	Lost
44613	W	F	36	Adenocarcinoma	Left breast	Radical amputation	Spine, ribs	33 months	9 months	Lost
42810	W	F	..	Adenocarcinoma	Left breast	Radical amputation	Ribs, pelvis, upper end of femur	1st op.: 42 mo. 2d op.: 21 mo.	Living after 1 mo.
42718	W	F	..	Scirrhous carcinoma	Right breast	Amputation of breast
41291	W	F	45	Carcinoma	Left breast	Radical amputation	Lower part of lumbar spine, pelvis and hip joints	60 months	34 months	X-rays	Living after 18 mo.
41231	W	F	..	Carcinoma breast	Radical amputation	Humerus, clavicle, pelvis	33 months	20 months	Living 24 mo., 1928
40830	W	F	63	Scirrhous carcinoma	Left breast	Radical amputation	4th and 5th lumbar vertebrae, pelvis, sacrum, upper part of femur	72 months	X-rays	Living 9 mo.
40716	W	F	45	Scirrhous carcinoma	Right breast	Radical amputation	3d and 4th lumbar vertebrae, right ilium, right sacroiliac joint	12 months	X-rays (24 times)	Living 12 mo., 1928
40585	W	F	70	Mollusary carcinoma	Right breast	Radical amputation	Bone (right leg)	Dead
40536	W	F	62	Scirrhous carcinoma	Left breast	None	Upper end of left femur, lower third of right femur, upper end of right femur	4 months	X-rays	Lived 2 mo., 4 wk.
40368	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	Skeleton
40002	W	F	42	Scirrhous carcinoma	Right breast	Radical amputation	Upper end of right femur, ilium	Femur below trochanter	2 weeks	Resection head, neck, right femur; X-rays	Lived 12 mo.
39788	W	F	39	Cystic adenoma, carcinoma	Left breast	Amputation of breast	Spleen	Dead
39923	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	2d lumbar vertebra	20 months	19½ months	X-rays	Living 10 mo., July, 1929

38850	W	F	36	Scirrhus carcinoma	Right breast	Radical amputation	Spine
38805	W	F	70	Scirrhus carcinoma	Left breast	Radical amputation	6th dorsal vertebra
38772	W	F	59	Scirrhus carcinoma	Right breast	Radical amputation	Upper end of right scerum, right ilium	12 months	Lost
38116	W	F	40	Scirrhus carcinoma	Right breast	Radical amputation	10th rib, left, posterior	79 months	2 1/2 months	X-rays	Lived 12 mo.	Lived 12 mo.
37870	W	F	45	Adenocarcinoma	Left breast	Amputation of breast	Skull, humeri, scapulae, clavicles, femora, all ribs, pelvis	8 months	2 or 3 mo.	Lived 12 mo.	Lived 12 mo.
37862	W	F	37	Fibrosarcoma	Right breast	Amputation of breast	4th and 5th cervical vertebrae	40 months	16 months	Lead and radium	Lived 9 mo.	Lived 9 mo.
37854	W	F	53	Scirrhus carcinoma, left breast	Left breast	Radical amputation	Left ischium, upper third of left femur	X-rays	Lived 26 mo. plus	Lived 26 mo.
37526	W	F	52	Scirrhus carcinoma	Left breast	Radical amputation	Skull, right sacro-iliac joint	Lead and X-rays	Lived 12 mo.	Lived 12 mo.
37192	W	F	33	Scirrhus carcinoma	Right breast	Radical amputation	Long bones	47 months	X-rays (?)	Lived 9 mo.	Lived 9 mo.
37166	W	F	54	Scirrhus carcinoma	Left breast	Radical amputation	Right humerus, right femur, ilia, vertebra	X-rays
36988	..	F	40	Carcinoma breast	Radical amputation	Left ilium, left iliac joint, acetabulum, upper third of left femur, upper third of right femur	Left ilium	36 months	X-rays	Lived 12 mo.	Lived 12 mo.
36727	W	F	56	Scirrhus carcinoma	Left breast	Radical amputation	5th dorsal, 4th and 5th lumbar vertebrae, ilia, acetabula, ischia, femora	X-rays	Lived 11 mo.	Lived 11 mo.
36004	W	F	..	Carcinoma	Right breast	Radical amputation	6th and 7th thoracic vertebrae	86 months	X-rays	Lived 5 mo.	Lived 5 mo.
35879	W	F	23	Carcinoma	Right breast	None	Skull, spine	24 months	Living 6 mo., 1916	Living 6 mo., 1916
35363	W	F	49	Carcinoma	Left breast	Not stated	Spine	36 months	24 months	X-rays	Lived 24 mo.	Lived 24 mo.
35120	W	F	51	Carcinoma	Right breast	Radical amputation	Right ilium, upper part of femur, 5th lumbar, 7th and 10th thoracic vertebrae, left femur, pelvis	57 months	X-rays	Lived 24 mo.	Lived 24 mo.
34980	W	F	42	Scirrhus carcinoma	Right breast	Radical amputation	Left sacro-iliac joint, left ilium, 5th and 6th thoracic vertebrae	27 months	9 months	X-rays
34938	Carcinoma	Right and left breasts	Amputation of breasts	Upper third of femur	Femur	Exploration, fracture wired	Lived 9 mo.	Lived 9 mo.

TABLE 1.—Cases of Carcinoma of the Breast with Metastases to Bone—Continued

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Metastases	Treatment of Metastases	Duration of Life Following Metastases
34100	W	F	..	Scirrhus carcinoma	Left breast	Amputation of breast	7th dorsal vertebra, cervical vertebra	8 months	7 months	Radium X-rays	Lived 9 mo.
33514	W	F	..	Carcinoma	Left breast	Amputation of breast	Pelvis	33 months	X-rays	Lived 23 mo.
33050	W	F	41	Scirrhus carcinoma	Right breast	Radical amputation	All lumbar vertebrae, sacrum, pelvis, hip joints	13 months	5 weeks	X-rays	Lived 6 mo.
32788	W	F	..	Carcinoma breast	None	Lower end of femur	Femur	56 months	Rest in bed X-rays	Living 12 mo., 1924 Living 19 mo.
32233	W	F	..	Cylindroma, carcinoma breast	Radical amputation	1st lumbar vertebra	Rest and splints for fractures	Lived about 14 mo.
31088	W	F	37	Scirrhus carcinoma	Right breast	Radical amputation	Right femur, humerus, ischium, left humerus, radius, femur, skull, cervical vertebrae	(1) left femur; (2) right femur	Lived 33 mo.
31050	W	F	44	Scirrhus carcinoma	Right breast	Radical amputation	Right femur, left femur, skull, ilium, vertebrae	Right femur	2 months	Few days	X-rays, Glover's serum	Lived 9 mo.
31273	..	F	45	Carcinoma	Left breast	Radical amputation	3d lumbar vertebra	16 months	X-rays	Lived 71 mo.
30116	W	F	50	Scirrhus carcinoma	Left breast	Radical amputation	2d lumbar vertebra	30 months	24 months	X-rays	Lived 48 mo.
30300	W	F	51	Scirrhus carcinoma	Right breast	Radical amputation	Left ilium	144 months	X-rays	Lived 29 mo.
30060	W	F	..	Scirrhus carcinoma	Right breast	Radical amputation	3d rib, anteriorly	75 mo. plus	72 months	Resection of rib tumor X-rays	Lived 21 mo.
29831	W	F	..	Colloid carcinoma	Left breast	Amputation of breast	Skull, ribs on right side
28821	O	F	50	Carcinoma, inoperable	Right breast	None	6th and 7th dorsal vertebrae, right clavicle, right scapula
28778	W	F	73	Carcinoma	Left breast	Radical amputation	Sternum	132 months plus	About 132 months
28510	..	F	21	Comedocarcinoma	Left breast	Radical amputation	Spleen	15 months plus	15 months	Lived 3 mo.

28465	W	F	47	Carcinoma, inoperable	Right breast	None	Skull, sternoclavicular joint	24 months	X-rays advised	Lived 17 mo.
27630	W	Carcinoma breast	Not stated	1st lumbar vertebra
20825	W	F	42	Scirrhus carcinoma	Right breast	Radical amputation	Left scapula, left humerus at junction of middle upper third	25 months	13 months	X-rays	Lived 11 mo.
20329	W	F	57	Carcinoma	Left breast	Radical amputation	10th thoracic vertebra, 7th, 8th and 9th ribs on right side, humeri, skull, femora	Multiple rib fractures	1st operation, 18 yr. 3 mo.; 2d operation, 2d operation, 3 mo.	Radium	Lived 26 mo.
26319½	W	F	..	Scirrhus carcinoma	Right breast	Amputation of breast	Skull, ribs, 11th thoracic vertebra	1st operation, 48 mo.; 2d operation, 22 mo.	Lived 19 mo.
23574	W	F	46	Scirrhus carcinoma	Right breast	Radical amputation	Lumbar spine, ribs	5 months
23559	W	F	42	Scirrhus carcinoma	Right breast	Radical amputation	Bone	50 months	8 months	X-rays	Lived 8 mo.
23091	W	F	40	Scirrhus carcinoma	Left breast	Radical amputation	Upper third of the femur, two ribs	Femur	55 months	34 months	Living 12 mo.
22550	W	F	45	Scirrhus carcinoma	Left breast	Radical amputation	Spine	120 months	108 months	Living 5 mo.
21266	W	F	50	Scirrhus carcinoma	Left breast	Radical amputation	Pelvic bones
19536	W	F	59	Scirrhus carcinoma	Right breast	Radical amputation	Long bones	Lived 1 mo. plus
18760	W	F	59	Inoperable carcinoma	Left breast	None	Vertebrae
18550	W	F	36	Scirrhus carcinoma	Left breast	Amputation of breast	2d lumbar vertebra	12 months	7 months	X-rays (three times)	Lived 5 mo.
18188	W	F	..	Scirrhus carcinoma	Right breast	Amputation of breast	5th, 6th, 7th and 8th thoracic vertebrae, skull	15 months	Lived 22 mo.
17629	W	F	63	Inoperable carcinoma	Left breast	Excision of breast	3d, 4th and 5th lumbar vertebrae, 4th and 5th ribs on right side	Spine explored	Lived 13 mo.
16998	W	F	45	Scirrhus carcinoma	Right breast	Excision of breast, later excision of axillary glands	Spine, skull	50 months	18 months
16406	W	F	46	Scirrhus carcinoma	Left breast	Radical amputation	Spine, right ilium	45 months	33 months	Lived 20 mo.

TABLE 1.—Cases of Carcinoma of the Breast with Metastases to Bone—Continued

Path. No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
10135	W	F	62	Scirrhous encephaloma	Left breast	Local excision of tumor, later radical amputation	3d rib, left	18 months	Exploration of rib
15894	..	F	49	Scirrhous encephaloma	Left breast	Radical amputation	Upper third of femur	Femur	19 months	8 months	Resection of head of femur	Lived 15 mo.
15646	W	F	37	Scirrhous encephaloma	Left breast	Radical amputation	Sternum	173 months	140 months	Radium
15318	W	F	45	Scirrhous encephaloma	Right breast	Radical amputation	Spine	54 months	18 months
15015	W	F	59	Medullary encephaloma	Left breast	Radical amputation	Spine
12701	W	F	37	Carcinoma	Right breast	None	Left tibia, sacrum, ilia, femora, skull	Lived 6½ mo.
11626	W	M	56	Colloid encephaloma	Right breast	Excision of tumor, later complete operation	Spine and entire skeleton	17 months	12 months	Lived 8 mo.
11177	W	F	40	Scirrhous encephaloma	Left breast	Radical amputation	Skull, left femur, left tibia, left ilium, lumbar vertebra	Left femur, 7 months 5 cm. below greater trochanter	A few days	Lived about 24 mo.
11169	W	F	49	Scirrhous encephaloma	Right breast	Radical amputation	Pelvis
11142	..	F	50	Scirrhous encephaloma	Right breast	Radical amputation	Spine
11063	W	F	68	Scirrhous encephaloma breast	Radical amputation	Spine
10251	..	F	32	Inoperable carcinoma breast	None	Pelvis, right femur	Femur	1 mo. (?)	Lived 1 mo. plus
9954	W	F	34	Scirrhous encephaloma	Left breast	Radical amputation	Lower end of femur	Femur	13 months	10 months	X-rays
9839	W	F	32	Scirrhous encephaloma	Right breast	Radical amputation	Spine
8922	W	F	58	Scirrhous encephaloma	Left breast	Radical amputation	4th lumbar vertebra	24 months	18 months	Lived 36 mo.
8886	W	F	60	Scirrhous encephaloma	Left breast	Radical amputation	Spine

No.	Sex	Age	Disease	Operation	Side	Time	Result
8175	W	F	57	Scirrhus carci- noma	Right breast	Bone
7261	W	F	55	Scirrhus carci- noma	Right breast	Spine
6470	W	F	70	Scirrhus carci- noma	Left breast	Sternum
6405	W	F	33	Carcinoma breast	11th and 12th dorsal vertebrae Lived 2 mo.
6318	W	F	42	Carcinoma	Left breast	Thoracic vertebra
6300	W	F	45	Scirrhus carci- noma	Left breast	Spine Lived 5 mo.
5939	W	F	32	Carcinoma	Right breast	Vertebra Lived 4 mo.
5361	Medullary carci- noma	Left breast	Hip Lived 12 mo.
5144	W	F	39	Comedocarcinoma	Right breast	3d thoracic vertebra Lived 3 mo.
4726	W	F	..	Scirrhus carci- noma breast	Spine
4495	W	F	62	Scirrhus carci- noma	Left breast	Spine
4473	W	F	48	Scirrhus carci- noma	Left breast	Sternum, ribs
4305	W	F	50	Comedocarcinoma	Right breast	Skull, thoracic and lumbar spine Lived 3 mo.
3759	W	F	45	Carcinoma	Left breast	Upper third of right humerus Lived 18 mo.
2853	W	F	34	Scirrhus carci- noma	Right breast	Spine
3538	W	F	39	Scirrhus carci- noma	Left breast	Spine
611	W	F	61	Scirrhus carci- noma	Right breast	Left femur Lived 6 mo. plus
260	W	F	59	Carcinoma	Right breast	Femur Lived 8 mo. plus
93	O	F	60	Medullary carci- noma	Left breast	Left femur Lived 6 mo.
92	W	F	46	Scirrhus carci- noma	Left breast	Head of femur Lived 6 mo. plus

carcinoma of the bone, making a total incidence of 100 cases (table 1), or 5.2 per cent of all carcinomas of the breast in this study. Many of the patients living to date have not reached the five year period, and only the future can predict their clinical course.

Metastatic cancer from the breast in bone is a disease occurring in middle or late life. The majority of the lesions occur between the ages of 35 and 55, the extremes in age being 21 and 73 (fig. 1).

The bones most frequently involved are those of the spine, pelvis, femur, skull, ribs and humerus in the order given (table 2, fig. 2).

TABLE 2.—*Involvement of Bone in One Hundred Cases of Metastatic Carcinoma of the Breast*

Bone Involved	Number of Cases	Number of Times	Right	Left	Undetermined
Spine					
Cervical.....	3	2	1
Thoracic.....	13	23	2
Lumbar.....	14	17	2
Femur					
Upper third.....	16	20	7	8	5
Lower third.....	4	4	2	..	2
Head.....	2	3	1	1	1
Pelvis					
Ilium.....	15	19	8	8	3
Ischium.....	5	7	3	3	1
Sacrum.....	3	3	1	..	2
Sacro-iliac joint.....	3	3	2	1	..
Acetabulum.....	2	3	1	2	..
Pubes.....	1	2	1	1	..
Skull (frontal, parietal, temporal).....	13	15	10
Ribs.....	13	10	4	2	7
Humerus					
Upper third.....	2	2	1	1	..
Head.....	2	3	2	1	..
Junction of middle and lower third....	1	1	1
Junction of middle and upper third....	1	1	..	1	..
Sternum.....	4	4
Entire skeleton.....	3	Multiple
Clavicle.....	3	4	2	2	..
Scapula.....	3	4	2	2	..
Tibia (upper third).....	1	1	..	1	..
Radius (lower third).....	1	1	..	1	..

While metastases were rarely found in the bones of the forearm and the lower part of the leg,² two such incidences are noted: one in the upper end of the tibia and the other in the lower end of the radius.

Prior to 1910, accurate information concerning the location of metastases was gained by necropsy and physical examination. In general, these statistics afforded only a trustworthy evidence in bones that were the common site of pathologic fracture, or that were easily accessible at the postmortem table. With the advent of the x-rays, roentgenograms

2. Osler, W.: Medical Aspects of Carcinoma of the Breast, Brit. M. J. 1:1, 1906. Neal, M. P., and Robnett, D. A.: Generalized Osseous Metastases Secondary to Atrophic Scirrhus Carcinoma of Left Breast, Arch. Surg. 14:529 (Feb.) 1927. Carnett and Howell (footnote 1, third reference). Handley (footnote 1, fourth reference).

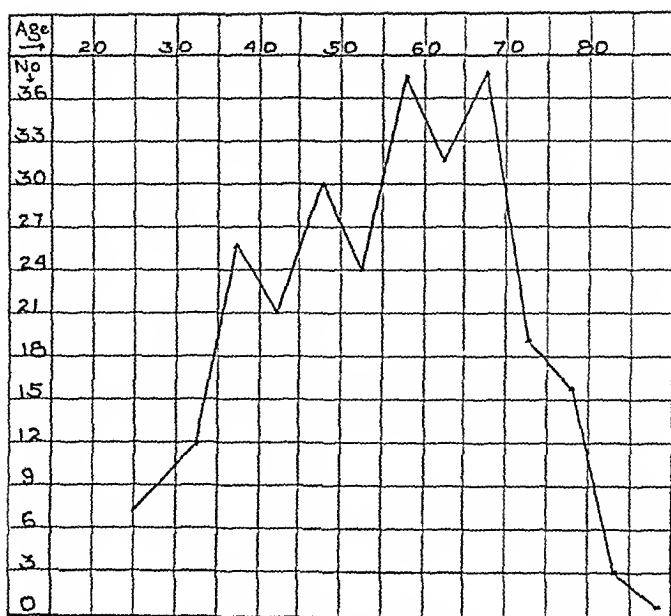


Fig. 1.—Age incidence of metastatic carcinoma and metastatic sarcoma in 339 cases with secondary involvement of the bone.

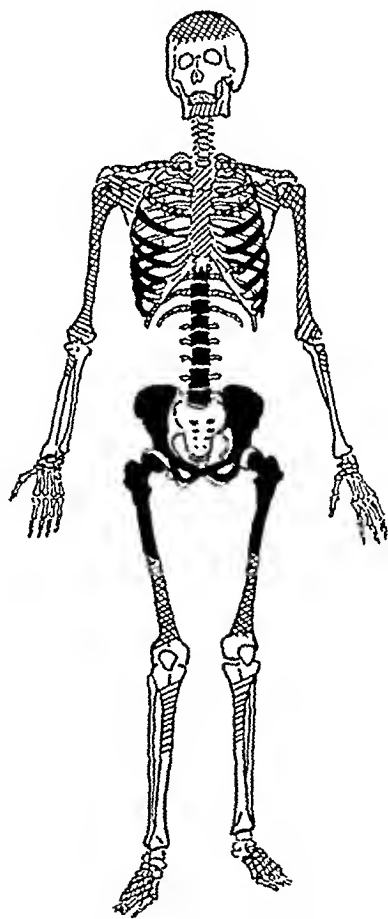


Fig. 2.—Distribution of carcinoma and sarcoma with metastases to bone according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites; the diagonal lines, the occasional sites, and the white areas, rare sites.

of the entire skeleton have permitted greater accuracy and have facilitated the study of the incidence of bony metastases in various parts of the skeleton. However, many bones, such as the sternum and ribs, can be demonstrated microscopically to be invaded by tumor, although the evidence may not appear in the roentgenograms. A comparison of statistics deduced by the older methods of examinations and those of more recent studies which are made up largely of roentgenologic examinations shows the greater value of the combined methods (table 3).

Symptoms.—Clinically, pain of a severe rheumatic character is an important feature. When these metastatic foci localize about the spine,

TABLE 3.—*Incidence of Bony Metastases*

	100 Cases*		73 Cases†	
	No. of Cases	Percentage of Total	No. of Cases	Percentage of Total
Spine.....	30	30	12	3.6
Pelvis.....	29	29	0	0.0
Femur.....	22	22	14	4.2
Ribs.....	13	13	23	8.0
Cranial bones.....	13	13	9	2.7
Humerus.....	6	6	9	2.7
Sternum.....	4	4	30	9.0
Clavicle.....	3	3	5	1.5
Scapula.....	3	3	1	0.3
Radius.....	1	1	0	0.0
Tibia.....	1	1	1	0.3
Ulna.....	0	0	0	0.0
Fibula.....	0	0	0	0.0
Patella.....	0	0	1	0.3
Bones of hand.....	0	0	1	0.3
Bones of foot.....	0	0	0	0.0

* From the Surgical Pathological Laboratory, 1930.

† From Sampson Handley: *Cancer of the Breast and Its Operative Treatment*, 1906.

girdle pains and neurologic manifestations, such as extramammary pain,³ abdominal pain and pain in the sciatic nerve, numbness of the legs or arms, spastic paralysis or weakness of the various extremities are present. Loss of vesical control and weakness of the rectal sphincters are not infrequent signs. Often there are pains about the head associated with involvement of the skull, and two cases showed ocular changes, one unilateral exophthalmos and the other bilateral choking of the disks. Metastatic deposits in the extremities themselves often give severe, boring pains—stiffness of adjacent joints and swelling of the affected limb.

In the beginning, pain may be so mild and transient that it attracts little notice, and only after more ominous symptoms appear is medical

3. Ginsburg (footnote 1, seventh reference).

aid sought. The patient may be seized at the onset with excruciating pains requiring large doses of morphine, and occasionally pain precedes roentgenologic evidence of bony metastases from three to eighteen months.³

Pathologic fracture occurred in fifteen instances (15 per cent). Thirteen were in the femur, one in the ilium, and another case revealed multiple fractures of the ribs. As was pointed out in a previous communication,⁴ among the malignant tumors of bone the greater number of pathologic fractures (62 per cent) were found in association with multiple myeloma, while other types of neoplastic lesions in bone similarly affected by fracture are, in the order of their frequency: cyst of the bone, 45 per cent; giant cell tumor, 14 per cent; osteogenic sarcoma, 8 per cent; and Ewing's sarcoma,⁵ 5 per cent.

Patients show great variability in their constitutional response to invasion by the tumor. In some cases a rapid progress of the disease is noted with little or no attempt on the part of the body to react; while in others, with the assistance of various therapeutic aids, improvement occurs, and the patients are able to live useful lives for some time.

The blood picture is normal in most cases of early bony metastases; the majority of them eventually show a secondary type of anemia with its complications as the disease progresses. The leukocyte count is practically normal, save for a slight eosinophilia in a few instances—from two to four eosinophils per hundred cells. In the literature⁶ an occasional case with bony metastases is reported, showing a pseudopernicious type of anemia with a color index over 1, a slight leukocytosis, nucleated red blood cells, myelocytes and myeloblasts. The ordinary anemia of cancer, according to Piney,⁷ is not dependent on the presence of carcinomatous deposits in the marrow but on intrinsic changes in this tissue. Blood changes simulating those in pseudopernicious anemia have always been found in cases in which metastasis has been present for a sufficient time to permit hyperplasia of the marrow. Chemical examination shows that the blood is normal in most patients. An occasional trace of albumin is found in the urine, and in three cases Bence-Jones bodies were isolated.

4. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, *Arch. Surg.* **16**:818 (April) 1928.

5. Copeland, M. M., and Geschickter, C. F.: Ewing's Sarcoma, *Arch. Surg.* **20**:258 (Feb.) 1930.

6. Epstein, J.: Blutbefunde bei metastatischer Carcinöse des Knochenmarks, *Ztschr. f. klin. Med.* **30**:121, 1896. Houston, T.: The Conditions that Simulate Pernicious Anemia, *Brit. M. J.* **2**:1257, 1903.

7. Piney, A.: Carcinoma of the Bone Marrow, *Brit. J. Surg.* **10**:235, 1922-1923.

The terminal phases of the disease reveal a progressive *emaciation*, often with much pain, and when the lungs are involved (nineteen cases), respiratory embarrassment with spitting of blood and paroxysms of coughing supervenes.

Internal metastases usually present themselves later than the secondary deposits to bone.

Roentgen Studies.—As depicted by the roentgenogram, lesions of metastatic carcinoma of the breast which have localized in the bone are most often multiple, presenting themselves as a single focus in only one fourth of the cases. The majority of these solitary metastases are in



Fig. 3 (path. no. 23091).—Roentgenogram of the upper third of a femur showing involvement of the greater trochanter and neck, one of the most frequent sites of metastases in this bone from carcinoma of the breast.

the vertebrae or femur, but it is very probable that if such cases were followed to their termination, lesions in other bones would appear.

Two types of metastatic lesions are noted in the x-ray films. The more common one is an osteolytic or bone-destructive lesion, while the other is a sclerosing or bone-forming process,⁸ the latter occurring in outspoken fashion only twice in this series of cases, although it is not uncommon in bony metastases from carcinoma of the prostate.

8. Plank, T. H.: An Unusually Interesting Case, *J. Radiol.* 4:247 (July) 1923. Ginsburg, S.: An Unusual Case of Osteoplastic Skeletal Metastases, *Arch. Surg.* 11:219 (Aug.) 1925.

When a long bone such as the femur is involved, the portion affected is usually the proximal end. In the femur, the metastases occur most frequently about the greater trochanter and surgical neck (fig. 3), producing destruction of the bone with little evidence of repair. There is practically no periosteal reaction, the lesion appearing initially as a medullary involvement with subsequent destruction of the cortex from within. It is interesting to note that often the focus of tumor in the femur is well above the average entrance of the nutrient artery,⁹ a fact cited by Handley¹⁰ in favor of lymphatic permeation as a mode of metastases. This will be discussed subsequently.



Fig. 4 (path. no. 31650).—Involvement of the greater trochanter, neck and upper shaft of a femur showing increased density of the bone within the areas of destruction.

Sometimes mottling due to increased density of the bone occurs within the area of destruction (figs. 4 and 5), and a thickening of the cortex appears above or below the site of metastasis. This increase in density is found microscopically to be an attempt at repair of the bone or fibro-ostosis.¹¹ This reaction is often marked after roentgen therapy over the affected bone.

9. Sobotta, J., and McMurrich, J. P.: *Atlas of Human Anatomy*, New York, G. E. Stechert & Company, 1927, vol. 1, pp. 1-98.

10 Handley (footnote 1, fourth reference).

11. Geschickter, C. F., and Copeland, M. M., with Foreword by Bloodgood, J. C.: *Osteitis Fibrosa and Giant Cell Tumor*, *Arch. Surg.* 19:169 (Aug.) 1929.

Bloodgood¹² has pointed out that evidence of such formation of new bone may be used as a point in differential diagnosis in multiple tumors of the bone. When this formation occurs as mottling within an area of destruction in the bone, it favors the presence of a metastatic process as opposed to the more definitely punched-out areas of destruction seen in such lesions as multiple myeloma.

When the pelvis is implicated, the heads of the femurs may be involved, due to an extension of tumor from the pelvis along the ligamentum teres (fig. 6). The significance of such an associated involvement will be pointed out later in a discussion of the modes of metastases.



Fig. 5 (path. no. 35420).—Mammary carcinoma involving the greater trochanter and upper shaft of a femur with thickening of the cortex below the lesion and evidence of the formation of new bone within the area of destruction.

The entire femur may be involved with the riddling of the other bones, or rarely isolated deposits of tumor may appear in the lower third (fig. 7). The humerus, though less frequently affected, shows the same type of destruction either in the head, in the region of the nutrient artery which is located medially and opposite the attachment of the deltoid muscle, or in the bone, which may be diffusely involved.

12. Bloodgood, J. C.: *Bone Tumors, Benign and Malignant: A Brief Summary of the Salient Features Based Upon the Study of Some Three Hundred and Seventy Cases*, *Am. J. Surg.* **34**:229 (Sept.) 1920.

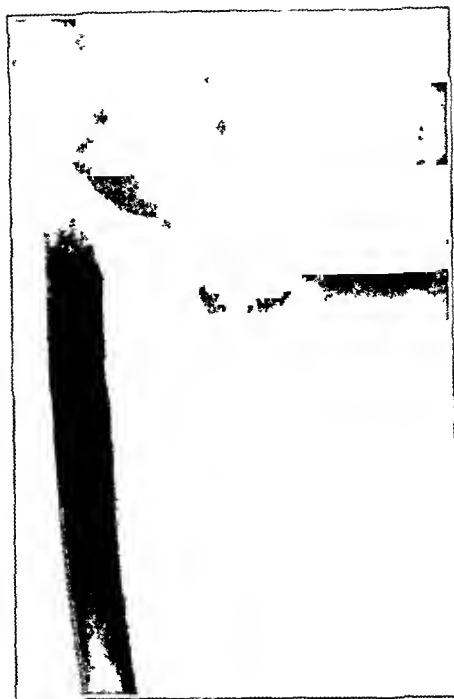


Fig. 6 (path. no. 40002).—Roentgenogram of the pelvis and upper third of a femur showing the associated involvement of pelvis and femur which is due to an extension of the tumor from the pelvis along the ligamentum teres.

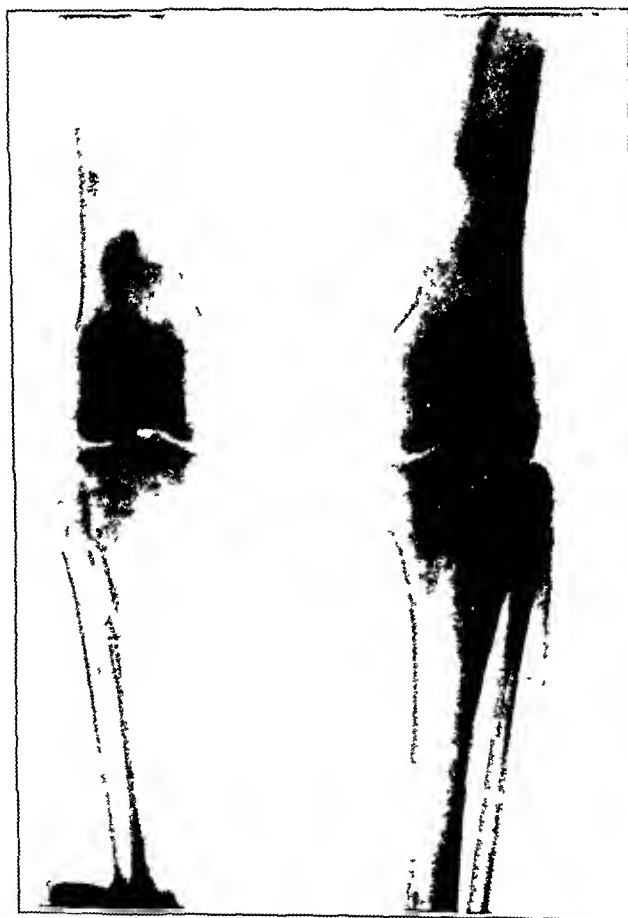


Fig. 7 (path. no. 31688).—Roentgenogram of the lower third of a femur showing involvement of the inner aspect of the lower shaft.

Recently, Carnett and Howell¹³ have shown that the humerus together with the shoulder girdle is affected more frequently than has been found in the present series. But among the cases studied by these authors, radical operation for the complete removal of the breast was rare, whereas in the series of cases from this laboratory, 75 per cent were subjected to the radical operation from four to eighteen months before metastases appeared. In the cases that received radical operation, the greater part of the lymphatic drainage adjacent to the seat of the primary tumor was interrupted, and the likelihood of a regional spread of the disease was greatly reduced.

The pelvis, vertebrae, skull, ribs, scapula, clavicle and sternum, which represent the other bones usually affected, showed the same typical medullary destruction with punched-out areas not unlike those seen in multiple myeloma (figs. 8 and 9). The tendency of these areas to become confluent and to be fringed by bone of increased density is frequent when the involvement of the skeleton is diffuse. In such cases the lack of distortion or bending of the bones, despite the degree of pathologic change, is outstanding. Failure for such distortion to take place is due partially to the advanced stage of the disease which confines the patient to bed, and to the fact that roentgen therapy is so frequently resorted to; also, the age of the patient is responsible for a degree of brittleness of the bones which makes fracture rather than bending the rule. In one case, the lower end of the radius showed a punched-out area in its lower portion near the region of the epiphyseal line and on the medial side of the bone. Above it, a slight irregular mottling is noted in the cortical and medullary area (fig. 10).

Solitary areas of metastatic carcinoma may be simulated by a latent cyst of the bone (fig. 11), a solitary focus of multiple myeloma (fig. 12) or by the osteolytic form of osteogenic sarcoma (fig. 13). The latent cyst of the bone is to be distinguished from metastatic carcinoma by the distinct signs of ossification present in the bone shell, and the thickness and competent defensive reaction visible in the areas surrounding the walled-off cavity. The latent cyst of the bone is nearly always without symptoms clinically, whereas pain and dysfunction of the part occur as a rule with the metastatic lesion.

In the roentgenogram it may be practically impossible to distinguish between multiple myeloma and diffuse metastatic carcinoma. Both may be central destructive lesions of the bone which gradually erode the cortex from within outward. Bence-Jones bodies in the urine in cases of multiple myeloma, 65 per cent, however, occur more frequently than in cases with metastatic carcinoma from the breast, 4 per cent.

13. Carnett and Howell (footnote 1, third reference).



Fig. 8 (path. no. 37870).—Roentgenogram of the upper third of a humerus with the other bones of the shoulder girdle and ribs, showing punched-out areas not unlike multiple myeloma.



Fig. 9 (path. no. 37870).—Skull showing metastases from carcinoma of the breast simulating multiple myeloma.



Fig. 10 (path. no. 31688).—A lesion in the lower end of the radius represented by a punched-out area in the region of the epiphyseal line and on the medial side of the bone.



Fig. 11 (path. no. 42526).—A latent cyst of the bone in the lower end of a tibia which may be confused with solitary areas of metastatic carcinoma.

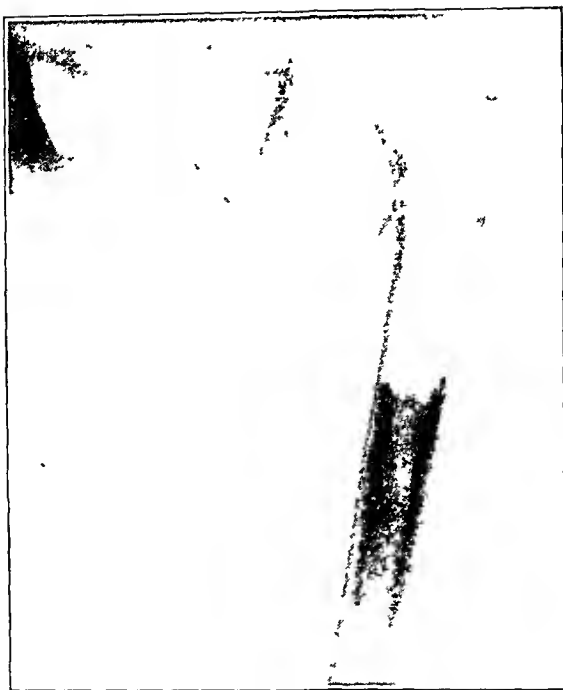


Fig. 12 (path. no. 42108) —A solitary focus of multiple myeloma which may be confused with metastatic carcinoma when it is situated in a bone as a single lesion

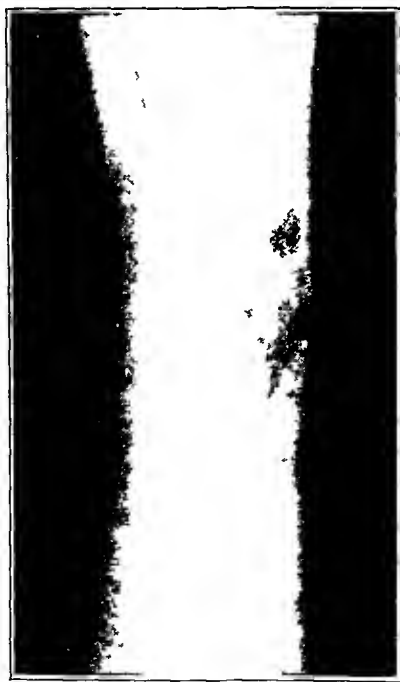


Fig. 13 (path. no. 37614).—Roentgenogram of a femur showing the osteolytic form of osteogenic sarcoma, not infrequently confused with the roentgenographic picture of metastatic carcinoma.



Fig. 14 (path. no. 37870).—A longitudinal section of a humerus showing involvement by metastatic mammary carcinoma. A cyst may be seen in the upper shaft filled with dark, pigmented, jelly-like material.



Fig. 15 (path. no. 40002).—A longitudinal section of the upper third of a femur showing areas of metastatic carcinoma just beneath the minor trochanter where pathologic fracture had occurred, and in the region of the fovea capitis other deposits are seen.

The osteolytic type of osteogenic sarcoma may produce an area of destruction of the bone similar to that in metastatic carcinoma. Such an area shows a greater inclination to be asymmetrically located in the bone and shows evidence of its more rapidly destructive character.

Pathologic Changes.—Of the gross material at hand, the femur and the humerus offer the most valuable information in the interpretation of the roentgen observations, and in analyzing the modes of metastases.

The humerus is involved principally in the medullary and cortical areas (fig. 14), the medullary cavity in the upper portion of one

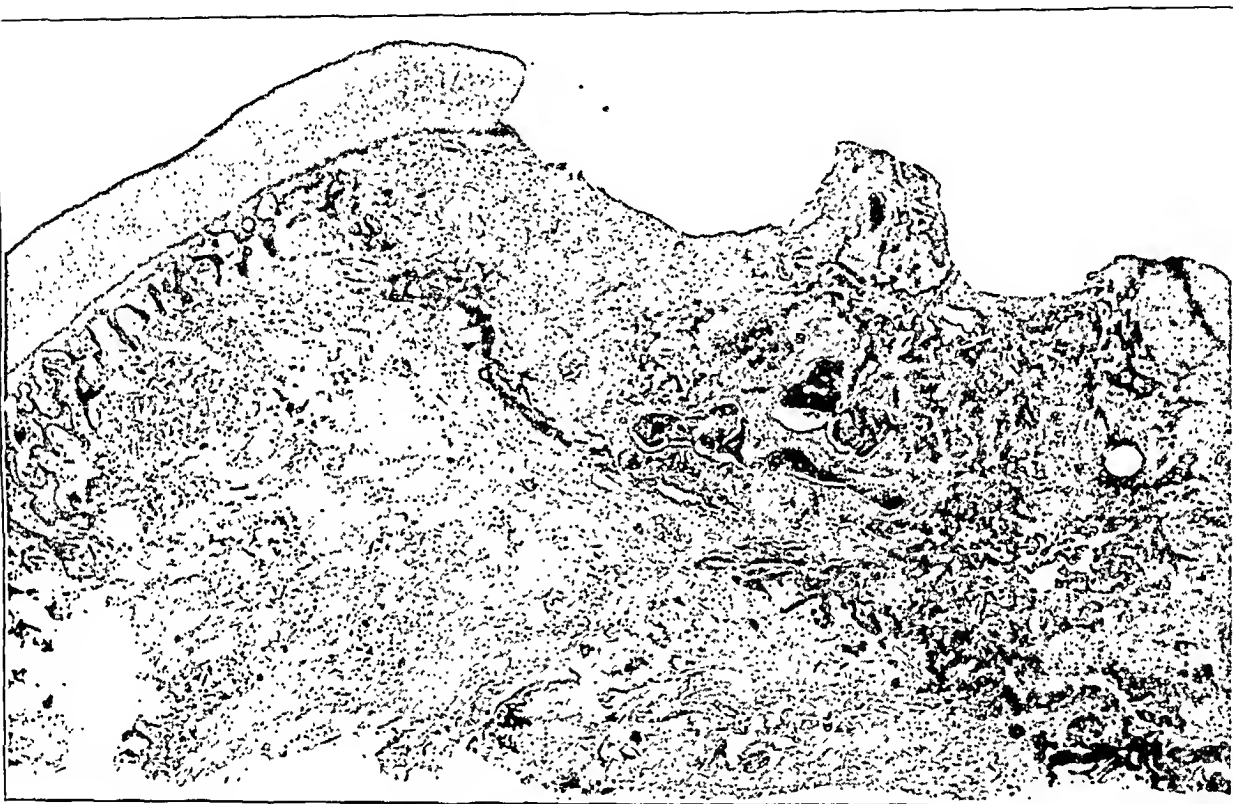


Fig. 16 (path. no. 40002).—Low power photomicrograph of an area in the region of the fovea capitis taken from the head of the femur depicted in figure 15. Note the infiltration of epithelial cells from above downward and the area of fibrous tissue reaction below the tumor invasion. The joint cartilage is intact on either side of the tendinous attachment.

humerus being practically replaced by carcinomatous tissue, the tumor extending well up into the head with discrete tumor nodules appearing in the spongy bone just beneath the articular cartilage. Below the region of the greater tuberosity, the entire cortex is destroyed, while rather substantial bone is found in the region and just medialward to this point. In the upper shaft of the bone, a cystic area with a chocolate colored wall is seen, the result of the absorption of hemorrhage.

In one instance, the majority of the deposits of tumor were found in the upper portion of the head around the greater tuberosity and beneath the articular cartilage extending down toward the shaft, interrupted by a rather well preserved area of spongy bone. Beneath this area of

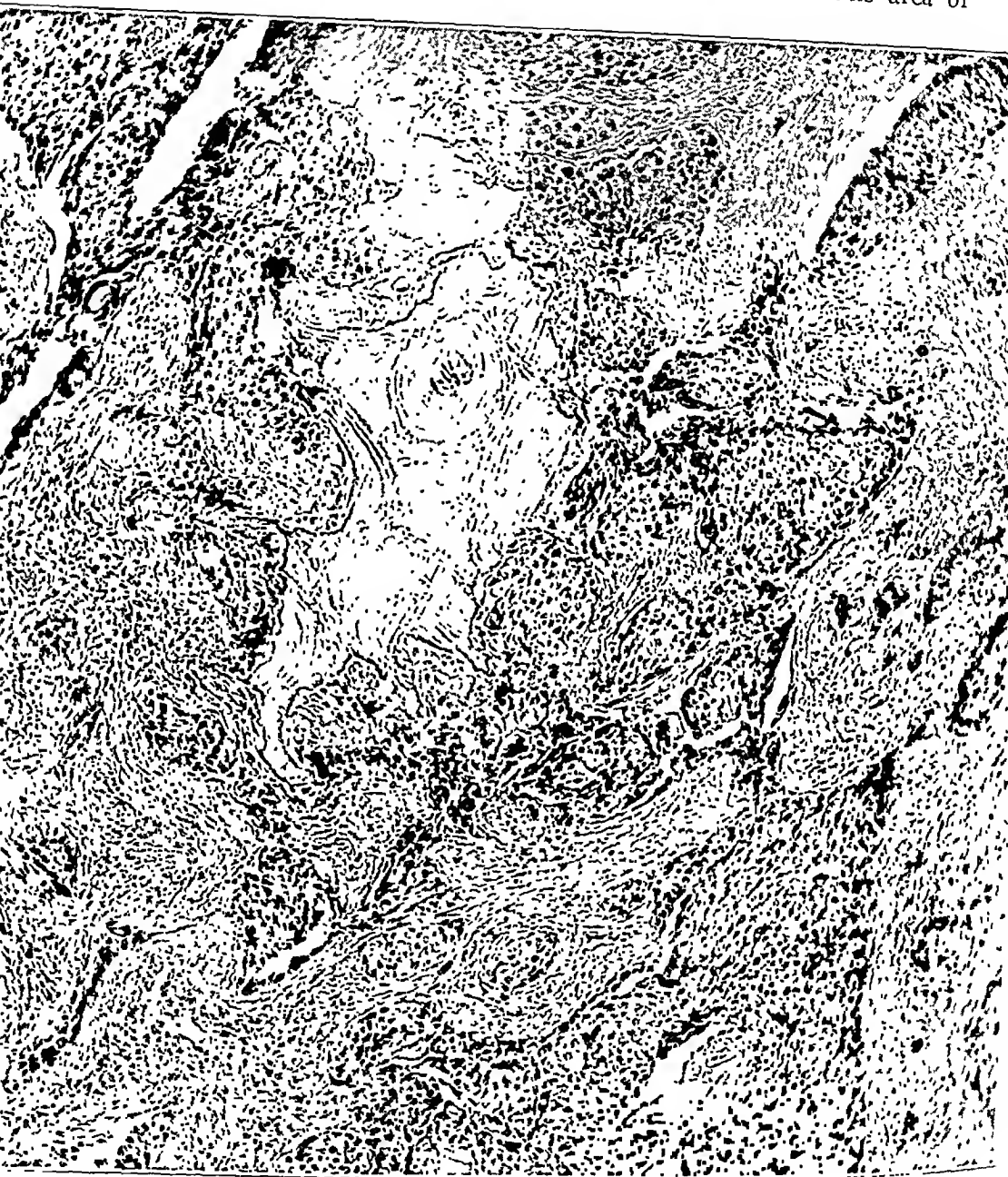


Fig. 17 (path. no. 40002).—Photomicrograph showing nests of epithelial cells in a fibrous stroma with occasional small spicules of old bone undergoing destruction by direct attack of the tumor cells.

spongy bone, further down in the shaft, the medullary cavity was found to be filled with tumor tissue, the vertebrae in this case showing focal deposits in the peripheral portion of the bone.

The femur most often showed metastases in the head and in the region of the great tuberosity with extension down into the shaft. In one case, a pathologic fracture had occurred just beneath the minor trochanter, at which point a cellular area of tumor deposit existed. In the region of the fovea capitis, another cellular deposit was found (fig. 16) extending along beneath the articular cartilage down to the greater trochanter, the distance of which had been much shortened due to the telescoping of the head on the neck. Other femurs showed less extensive deposits in these same areas. The microscopic examination of sections taken from various points in these bones revealed destruction of the spongy and cortical bone by direct contact of the tumor cells with the bone and to a lesser extent by the activity of the osteoclasts destroying spicules of dead bone. Regardless of how the tumor cells reach the skeletal system, the progress in the bone seems to be via the medullary cavity and the haversian canals, beginning in those areas in which red marrow is present.

Sections taken from the head of the femur illustrated in figure 15 show large nests of epithelial cells in a fibrous stroma with occasional small spicules of old bone undergoing destruction by direct attack of the tumor cells (figs. 16 and 17).

Abundant evidence is found microscopically in favor of a natural tendency of bone to react by direct transition of fibroblasts to osteoblasts to osteoid tissue in an effort to protect itself from further invasion and to rebuild that part already destroyed (fig. 18). Areas of fibroostosis (a reaction to the invasion of cancer) are seen, with strands of fibrous tissue being transformed into osteoblasts and osteoid tissue, bordering on small nests of epithelial cells distributed throughout this reactive process. In cases in which roentgen therapy has been given with beneficial results, microscopic analysis of the affected bone reveals a marked increase in the fibrous tissue reaction and a transformation of this tissue into the osteoid type of bone. Cancer cells can be seen crowded between the fibrous strands (fig. 19).

Treatment.—A survey of the treatment received by patients with primary carcinoma of the breast and a study of the rate of dissemination of the cancer expressed in the interval of time between the first appearance of the tumor and metastases and also between the primary operation and the subsequent metastases throw some light on the results that can be obtained by resection alone or by resection and radiation or by radiation alone of the affected bones.

For purposes of analysis, the patients have been divided into the following groups: (1) those who first had a radical amputation of the breast; (2) those who had only simple amputation of the breast or local

excision; (3) those on whom no operation was performed and who only received various forms of palliative treatment.

In group 1 there are seventy-four patients with radical amputation of the breast, showing subsequent metastases to bone. The average

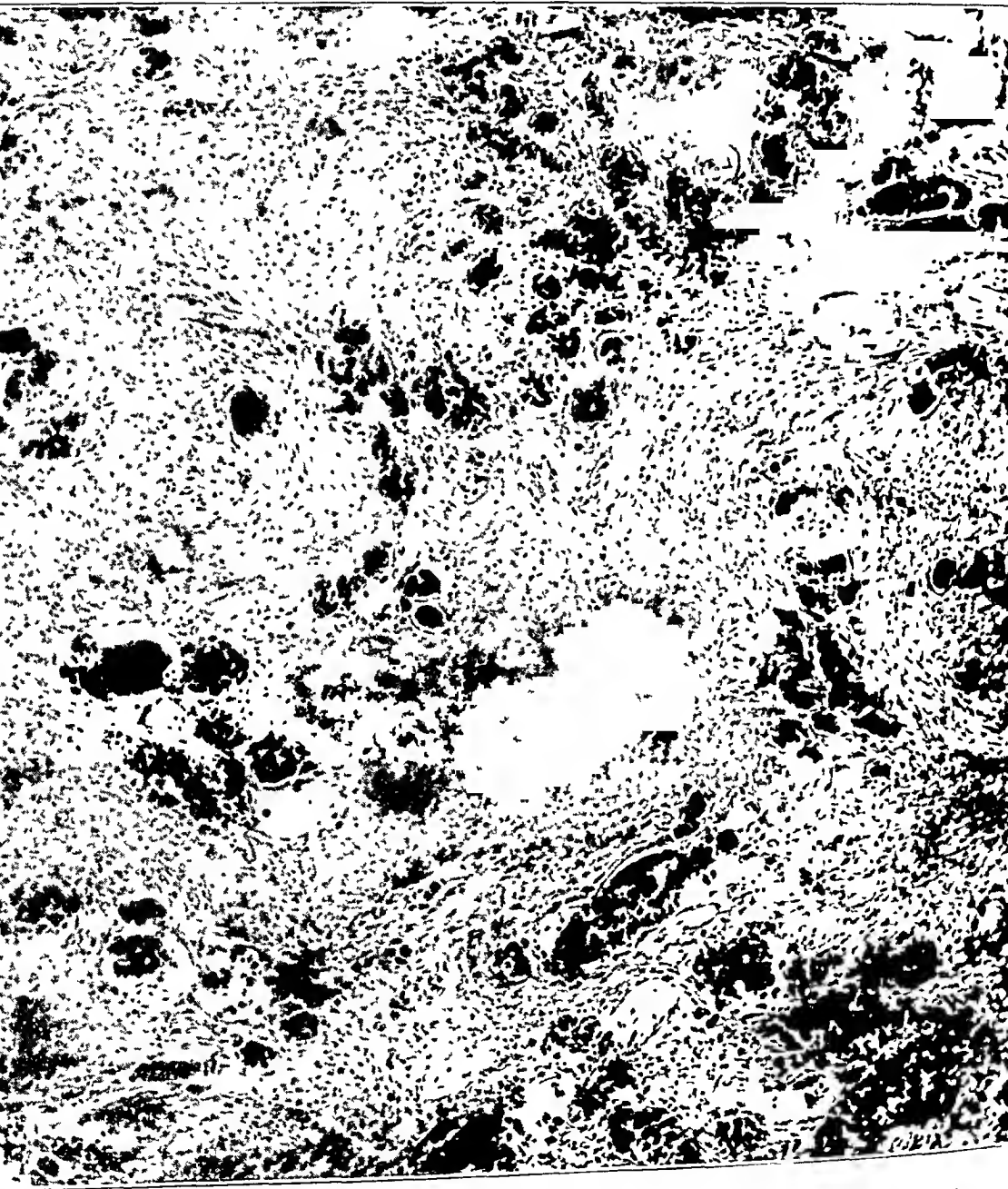


Fig. 18 (path. no. 12761).—Photomicrograph showing areas of fibro-osteosis with strands of fibrous tissue being transformed into osteoblasts and osteoid tissue, bordering on small nests of epithelial cells distributed throughout this reactive process.

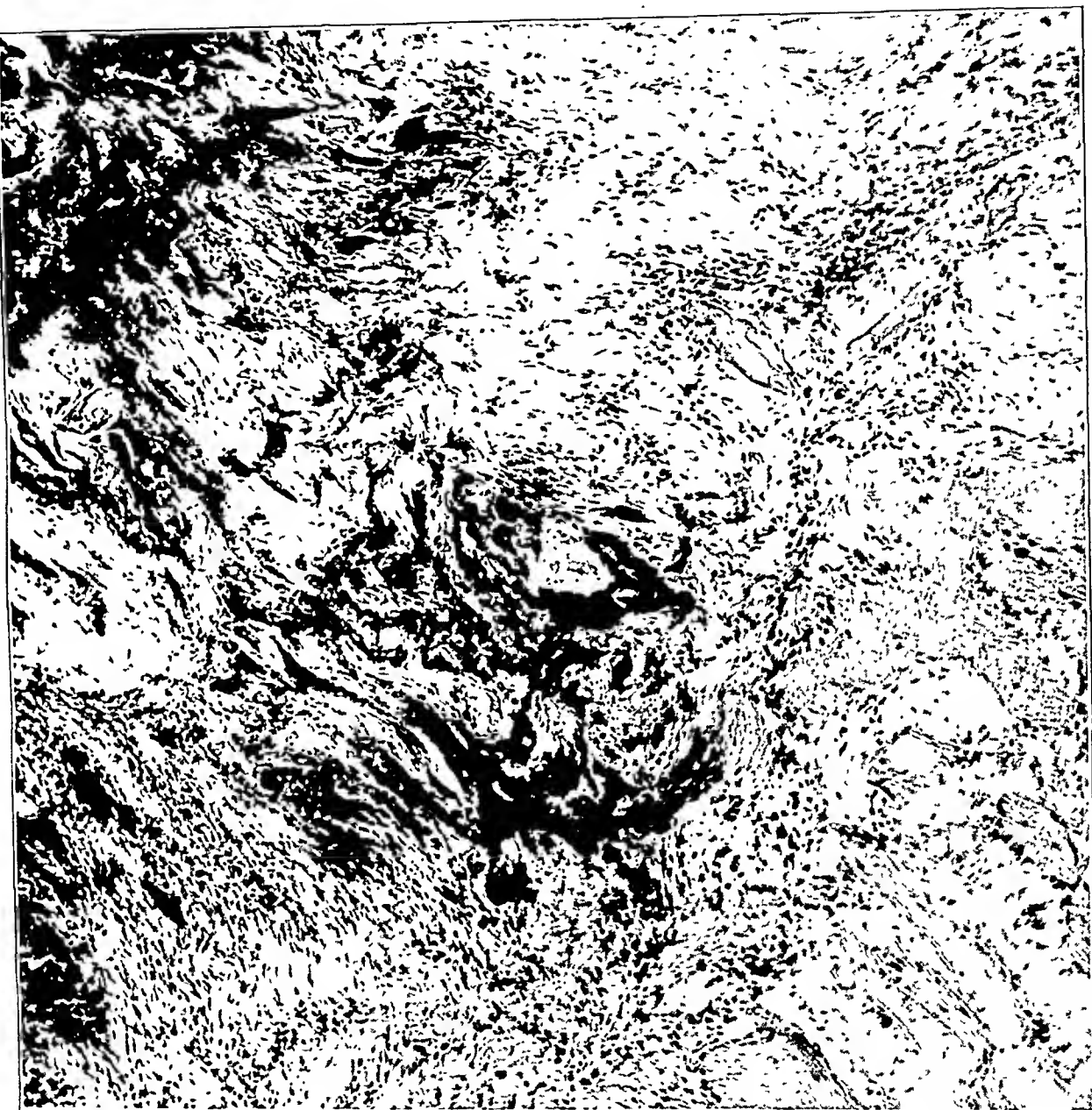


Fig. 19 (path. no. 34100).—Photomicrograph showing the effect of roentgen therapy on the structure of the bone invaded by tumor. Note the healing bone reaction (fibro-ostosis). Cancer cells can be seen crowded between the fibrous strands.

interval between the appearance of the primary tumor and the first evidence of metastases to bone was thirty-two and one-half months. In a few exceptional cases not included in this average, lesions of the bone developed at intervals as late as from nine to twenty years. If these exceptional cases are omitted, the time between radical removal of the breast and metastases averages thirty months. The tumors in the patients in group 1 were principally of the scirrhus type. Microscopic examination showed: scirrhus carcinoma, fifty-two cases; medullary carcinoma, four; comedocarcinoma, three; adenocarcinoma, three; and colloid carcinoma, one, with eleven unclassified.

Group 2 is represented by eighteen cases with a simple amputation of the breast or local excision. The average interval between the appearance of the primary tumor and the first evidence of metastases was twenty-nine and one-tenth months, while that between the operation and osseous involvement was sixteen and seven-tenths months. On microscopic examination, the histology of the primary tumors in this group were: unclassified, seven; scirrhus carcinoma, six; adenocarcinoma, three; colloid carcinoma, one, and fibrosarcoma, one.

Group 3, or the inoperable group, contained eight cases. The interval between the appearance of the primary tumor and the metastases ranged between one and twenty-four months.

The treatment as outlined here is based on the clinical experience of Drs. J. C. Bloodgood and Max Kahn. The roentgen treatment as given in this clinic consists of twelve thirty-minute exposures, using 200 kilovolts and 5 milliamperes, filtered through a combined 0.75 millimeter copper and 1 mm. aluminum filter, a 25 cm. diaphragmatic opening and 50 cm. focal distance. A total of ninety minutes is given over each area at periods of thirty minutes on consecutive days, each affected lesion being treated through four portals of entry. If further treatment is indicated, the foregoing procedure is repeated after a free interval of three months or more, depending on the condition of the patient.

While some of the treatments were given at other clinics, in the majority of instances the treatment was the equivalent of that given here, making the type of treatment fairly uniform in the various cases.

In group 1, those patients treated by radiation following the appearance of metastatic lesions of the bone had an average duration of life of eighteen months, two patients having survived the metastases for forty-eight and seventy-one months, respectively, while some lived as long as from one to two years. Among those not irradiated, the duration of life after metastases averaged eleven and one-half months.

In group 2, the average duration of life in persons with metastases who received roentgen treatment was sixteen and one-half months as compared with twelve and eight-tenths for those who did not receive irradiation.

In group 3, the patients who received radiation lived ten months, and those who did not receive radiation, seven and eight-tenths months.

Statistics on the various tumors metastasizing to bone show that the duration of metastases is essentially the same as in the aforementioned cases.

Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain which is experienced in the diseased bone.

A number of observers ¹⁴ reported favorable results from roentgenotherapy in metastatic carcinoma of the bone. Irradiation is effective both in relieving pain and in accelerating repair of the bone of the affected skeleton, apparently reducing the invasive powers, at least temporarily, of the deposits of the cancer. In this series of cases, many patients were relieved from pain for varying intervals of time, and in four cases marked formation of new bone was noted with relief from pain and increased usefulness of the affected bone.

It would seem, therefore, that patients with carcinoma of the breast metastasizing to bone, when treated by roentgen therapy, may expect relief from pain and often a few months of fairly comfortable living, thus making the procedure one of definite benefit. In refractory cases, resection of the affected portion of the bone, where feasible, may be indicated for the relief from pain.

HYPERNEPHROMA

The great majority of hypernephromas are primary in the substance of the kidney, although they may develop in other regions.¹⁵ Grawitz, in 1879, was one of the first to describe such a tumor,¹⁶ and in 1898 the term hypernephroma was applied to the neoplasm by Birch-Hirschfeld.¹⁷

There is a feeling among pathologists that hypernephroma has a special predilection for the bones, but from an investigation of the literature it is difficult to form any definite idea as to the incidence of osseous involvement.

14. Levin, I.: The Prognostic and Therapeutic Significance of Skeletal Metastasis in Cancer of the Breast, *Ann. Surg.* **65**:326, 1917. Kelly, H. A., and Fricke, R. E.: Problems in Treatment of Carcinoma of the Breast, *Surg. Gynec. & Obst.* **38**:399, 1924. Ginsburg (footnote 1, seventh reference).

15. Gibson, A., and Bloodgood, J. C.: Metastatic Hypernephroma with Special Reference to Bone Metastases, *Surg. Gynec. & Obst.* **37**:490, 1923.

16. Grawitz, P.: Ueber maligne Osteomyelitis und sarkomatöse Erkrankungen des Knochensystems als Befunde bei Fällen von perniciöser Anämie, *Virchows Arch. f. path. Anat.* **76**:353, 1879.

17. Birch-Hirschfeld, F. V.: Sarkomatöse Drüsengeschwülst der Niere im Kindesalter, *Beitr. z. path. Anat. u. z. allg. Path.* **24**:343, 1898.

TABLE 4.—*Cases of Hypernephroma with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
49373	W	M	40	Hypernephroma	Right 6th rib	X-rays
42906	W	M	55	Hypernephroma	Upper end of right humerus	Humerus	X-rays, resection of upper end of humerus	Living 22 mo.
42704	W	M	26	Hypernephroma	Left ilium	X-rays, exploration	Living 3 mo.
38324	W	M	55	Hypernephroma	Bones of foot	Excision of part of tumor	Living 6 mo., 1926
37088	W	M	62	Hypernephroma	Upper third of right humerus	X-rays, amputation of right arm	Living 7 mo. 5 days, 1926
36524	W	M	66	Hypernephroma	2d, 3d and 4th right ribs, 6th thoracic and 3d lumbar vertebrae	2d, 3d and 4th right ribs	Supporting cast for back	Lived 6 mo.
35762	W	M	82	Hypernephroma	Lower end of right femur	Femur	Lived 9 mo.
35512	W	M	48	Hypernephroma	Tarsal and metatarsal bones of left foot	Exploration, amputation of left foot	Living 6 mo., 1924
35416	W	M	..	Hypernephroma	Upper end of right femur	Femur
34362	W	M	56	Hypernephroma	Upper end of right humerus	Amputation of right arm	Living 6 mo., 1921
32974	W	M	40	Hypernephroma	6th right rib	X-rays, biopsy
31887	W	F	52	Hypernephroma	Upper end of left femur, left ischium	Femur	Resection of head of femur, bone graft	Lived 10 mo.
30983	W	M	..	Hypernephroma	4th lumbar vertebra, right sacro-iliac joint, right ilium, skull, (parietal region)	X-rays, erysipelas and prodigious toxins (Coley's)	Lived 5 mo.
30631	W	F	69	Hypernephroma	Skull, right temporal bone, left parietal bone	Radium	Lived 34 mo.
29485	C	F	37	Hypernephroma	Upper end of femur	Femur
29461	W	F	55	Hypernephroma	Midshaft of right humerus	Humerus	Amputation of right arm	Lived 18 mo.
29397	W	M	28	Hypernephroma	All the lumbar vertebrae, all dorsal vertebrae, 2d cervical vertebra, 3d left rib, shaft of both humeri, upper end of femora	Lower end of femur	Hibb's operation
27964	W	M	30	Hypernephroma	Head, shaft, left humerus	Radium	Living 76 mo., 1927
6930	W	M	..	Hypernephroma	Humerus	Operation (?)
6290	W	M	52	Hypernephroma	Left sternum, upper end of femur, ribs	Femur
2250	W	M	45	Hypernephroma	Femur, humerus, dorsal vertebrae	Humerus
1415	Hypernephroma	Head of tibia

Among the sixty-three persons affected by hypernephroma registered in this laboratory, there are twenty-two instances (34.9 per cent) with metastases to bone (table 4). The age incidence ranges between 21 and 81; the peak of incidence is about the sixth decade. The bones usually affected in the order of their frequency are: humerus, spine, femur, pelvis, ribs, bone of foot, skull and sternum (table 5).

Symptoms.—The lesion of the bone may be the first indication of the presence of the tumor in the body, as illustrated by the following case report (fig. 20):

TABLE 5.—*Involvement of the Bone in Twenty-Two Cases of Hypernephroma*

Bone Involved	No. of Cases	No. of Times	Right	Left	Undetermined Side
Humerus					
Location (?).....	2	3	..	2	2
Upper third.....	4	4	3	1	..
Shaft.....	2	3	1	1	1
Femur					
Upper third.....	4	4	1	2	1
Middle third.....	1	1	1
Lower third.....	1	1	1
Spine					
Location (?).....	1	1	1
Cervical.....	1	1
Thoracic.....	3	13	1
Lumbar.....	3	7
Ribs	5	6	2	1	2
Pelvis					
Ilium.....	2	2	1	1	..
Ischium.....	1	1	..	1	..
Sacro-iliac joint.....	1	1	1
Bone of foot.....	2	1	..
Skull	2	3	1	1	1
Sternum	1	1
Tibia	1	1	1

A white man, aged 55, eleven years previously while in France had an attack of arthritis in the right shoulder which lasted one month; in addition, the left knee, both ankle joints, the wrists and the right elbow joint were involved. Following much needed dental work, the arthritic symptoms disappeared except during changes in the weather, when they continued to be present in the right shoulder.

Twenty months before presenting himself for examination, the patient began to have definite pain about the head of the right humerus, with slight limitation of motion in the right shoulder ten months later.

A roentgenogram was made in March, 1929, which showed an area of destruction of the upper shaft of the humerus just below the head, about the size of a silver dollar, mostly on the outer aspect of the humerus. In June, July and September, 1929, other roentgenograms were made showing the progressive nature of the destructive lesion. The first evidence of the pathologic fracture was noted

in the roentgenogram made in 1930 (fig. 20, *C*), associated with a fair-sized tumor of the soft part. Roentgen therapy had been administered in adequate doses on four occasions with some slight remission in the excruciating pain, but with no great relief. Considerable morphine was needed to allay the patient's suffering. Other bones in the body were examined but no significant defects were made out, nor were there symptoms suggestive of other lesions in the skeletal framework. Repeated examinations of the urine and of the blood revealed nothing abnormal

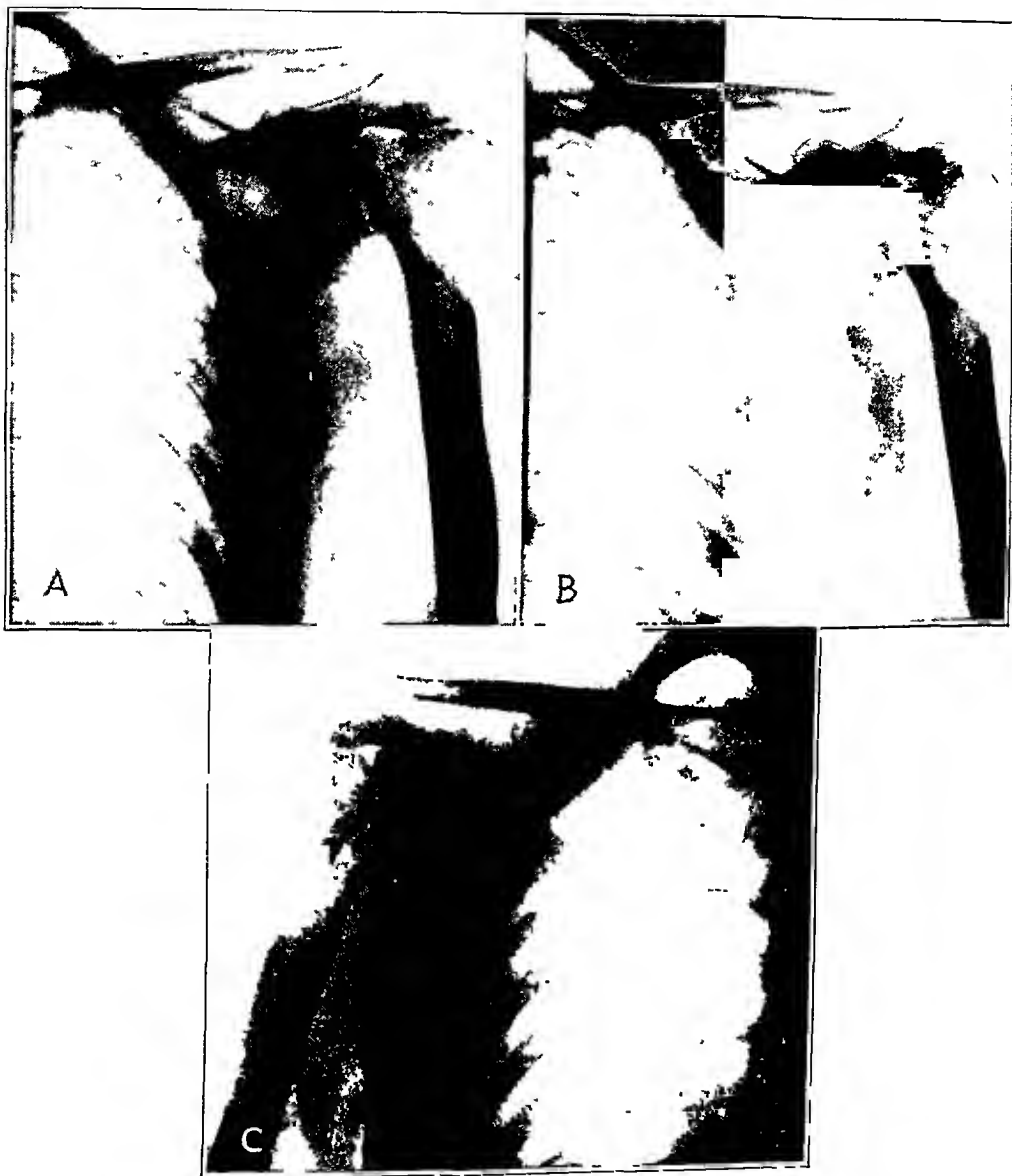


Fig. 20 (path. no. 42906).—*A*, roentgenogram of the upper end of a humerus showing marked destruction in the region of the surgical neck and upper shaft from metastatic hypernephroma. *B*, roentgenogram showing the progressive nature of the metastatic lesion in the head of a humerus taken three months after *A*. *C*, the complete destruction in the region of the surgical neck and the resultant pathologic fracture. This roentgenogram was taken about nine months following *A*.

In January, 1930, at a neighboring hospital, aspiration of the shoulder was done and only blood obtained. In May, 1930, Dr. Bloodgood resected the diseased head of the right humerus (fig. 21), which on microscopic examination (fig. 22) proved to be the seat of a hypernephroma. Operative recovery was uneventful, and before leaving the hospital the patient had practically abandoned the use of



Fig. 21 (path. no. 42906).—A gross specimen in longitudinal section showing metastatic tumor involvement from hypernephroma in the region of the surgical neck of a humerus, extending into the epiphysis, with total destruction of the cortex but no involvement of the joint cartilage. Note the subperiosteal invasion.

morphine, with complete relief from pain. Following the diagnosis of hypernephroma microscopically, a special examination was made of the kidneys, but no evidence of any lesion could be made out.

It has now been twenty-two months since the definite onset of symptoms, and the patient is doing very well.

Pathologic fracture occurred in ten cases (45.4 per cent), six times in the femur, three times in the humerus, and in one instance multiple fractures of the ribs were found. Most of the fractures occurred in the upper third of the long bones. In one instance, spontaneous pathologic fracture was the first symptom referable to the disease.

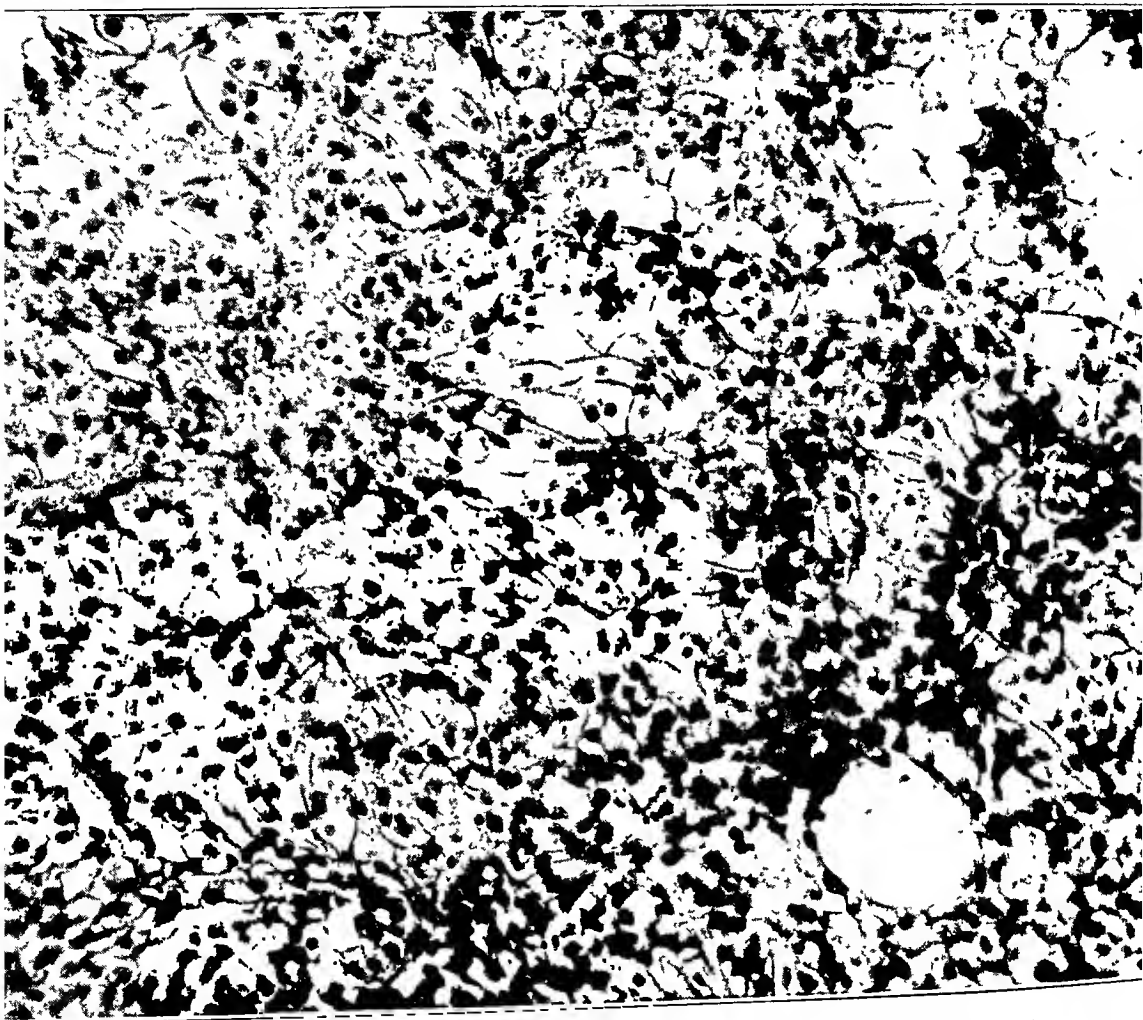


Fig. 22 (path. no. 42906).—Photomicrograph of the tumor depicted in figure 21, showing the typical structure of hypernephroma of the renal type, the cells are granular or foamy and the cytoplasm is remarkably clear. There is no evidence of fibro-ostosis.

As in metastases of the breast, the constitutional response of patients with metastatic hypernephroma of the bone is variable. True to the nature of metastatic lesions, pain of a rheumatic character is a leading symptom, and with spinal involvement many neurologic manifestations may be present. The blood picture eventually shows a secondary anemia, and the patients decline in weight, suffering from

progressively severe pains in the various bones affected. In three cases, the urine showed Bence-Jones bodies.

Roentgen Studies.—The lesions of the bone may appear in the roentgenogram either as single (fig. 20) or multiple lesions (fig. 23) located in one or more bones. In thirteen cases (59 per cent), the



Fig. 23 (path. no. 29397).—Multiple foci in the skeleton which may be seen in metastatic hypernephroma. *A*, roentgenogram of the upper end of a femur showing metastatic involvement with an associated lesion in the adjacent pelvis and a slight tendency toward the formation of new bone within the destroyed areas. *B*, tumor invasion of the upper shaft and head of a humerus. *C*, destruction of the lumbar-vertebrae with practically no tendency toward the formation of new bone within the destroyed areas.

secondary deposit of bone was found as a single focus; in the majority of cases it appeared in a long bone.

It is noteworthy that many of these lesions are at the site of the nutrient vessels (fig. 24) as well as in the head of the humerus (fig. 20, *A*) and femur, together with an associated lesion of the pelvis (fig. 23, *A*). There is no evidence in bony metastases from hypernephroma that any marked attempt at fibro-osteosis or formation

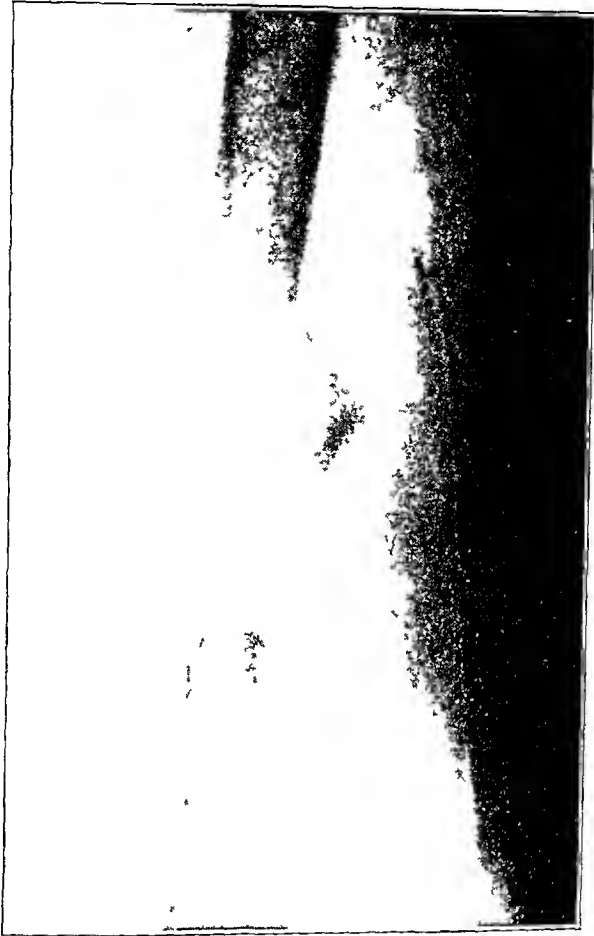


Fig. 24 (path. no. 29461).—A metastatic lesion depicted in the roentgenogram of a humerus at the site of the nutrient vessels showing marked destruction of the bone with expansion.

of new bone takes place within the area of destruction. The lesion is a destructive one in the shaft or the head of the long bones, and in the bodies of the vertebrae, in the membranous bones of the skull and in the small bones of the feet. The earliest sign of involvement is always a distinctly medullary defect which destroys the cortex from within, with little or no expansion. Although the growth readily extends into the soft parts, periosteal changes in the roentgenogram are an exception. In many instances, the viscera have not been invaded. It

is the impression in this laboratory that with small local growths of the tumor in the kidney there is a greater tendency toward dissemination to the bone, whereas larger local proliferations of the tumor are less likely to show skeletal involvement.

The differential diagnosis from the standpoint of roentgenology is similar to that of metastatic lesions of the bone in general, which have been detailed under carcinoma of the breast. In contrast to metastatic tumors from cancer of the breast, lesions of the bone in hypernephroma show a greater tendency to occur as a single focus and to be practically always osteolytic.

The gross appearance of the tumor as seen in the bone is well exemplified in figure 21. The growth always has a characteristic brownish-yellow color, flecked with red. When seen in the head of a long bone, there is marked destruction of the cortex with diffuse involvement of the medullary cavity and the spongy bone of the epiphysis. The cartilage of the joint does not seem to be affected, but the tumor pushes up beneath the periosteum in the area of cortical bone.

In the medullary cavity, in many cases, little deposits of brownish tumor can be seen. Where the shaft is involved at the site of the nutrient vessels (fig. 24), there is destruction of the cortex with tumor in the subperiosteal area, and at the attachment of the deltoid muscle which exerts a tensile influence on the bone, there is often evidence of a pathologic fracture with some invasion of the muscle tissue. Studies of the muscle tissue taken at points some distance from the site of invasion by the tumor reveal no tumor cells. This type of tumor occurring as a single focus lends proof to the embolic theory of metastases.

Further evidence is found in the literature to substantiate this mode of invasion of the bone. Albrecht¹⁸ reported a case in which there was a single lesion noted in the scapula four years after nephrectomy for hypernephroma. Ten years later, following resection of the scapula, the patient was still well. On the other hand, permeation of the lymphatics by tumor cells is undoubtedly a mode of progression in this tumor.¹⁹

The microscopic picture as seen in figures 22 and 25 is typical of the ordinary structure of hypernephroma of the renal type. There apparently is little tendency on the part of the bone to wall off the tumor. In a few areas there are spicules of old bone being destroyed by direct contact with the tumor cells. The cells are granular or foamy, and are interspersed with granules of lipoid. The cytoplasm is usually

18. Albrecht, P.: A Study of the Clinical and Pathological Anatomy of Hypernephroma, *Arch. f. klin. Chir.* **76**:1073, 1905.

19. LeCount, E. R.: Report of a Case of Malignant Hypernephroma, *Tr. Chicago Path. Soc.* **5**:82, 1901-1903. Bierring, W. L., and Albert, H.: Secondary Manifestations of Hypernephromata, *J. A. M. A.* **43**:234 (July 23) 1904.

remarkably clear, containing large globules of fat; the amount and clearness of the cytoplasm depends on the grade and rapidity of the growth.

Treatment.—The proof of the benefit of any one form of treatment depends on the ultimate result. In this group of cases of hypernephroma with metastases to bone, it has been difficult to follow many of the

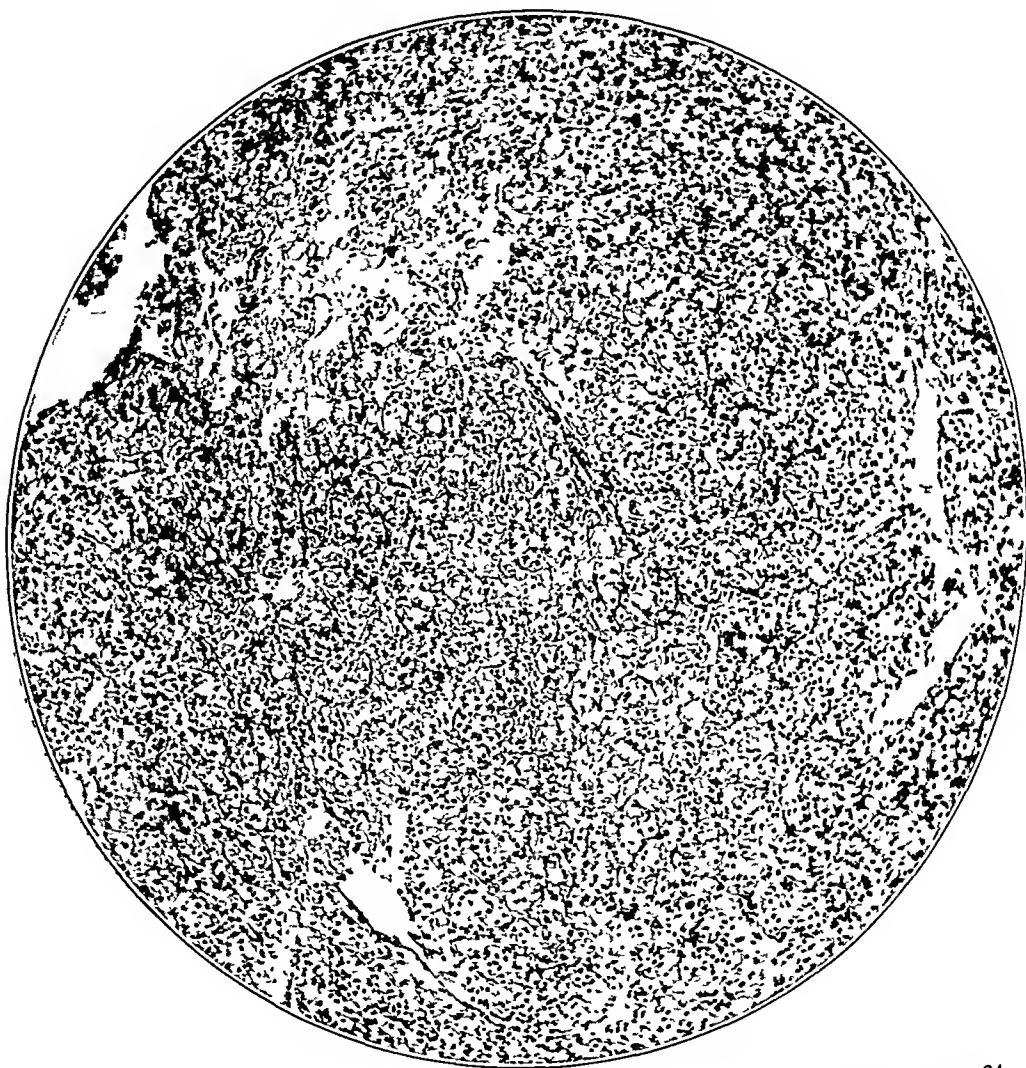


Fig. 25 (path. no. 29461).—Photomicrograph of the tumor shown in figure 24. Note the typical structure of hypernephroma cells with an occasional blood sinus. The cytoplasm of the cells is quite clear, and there is little evidence of stroma.

patients, but the data at hand point to the fact that irradiation alone offers as much for the prolongation of life as does surgical intervention alone or surgical measures combined with x-ray or radium therapy (table 4). One patient (path. no. 27964), who was treated by radium therapy, was living seventy-six months after the first symptoms of the tumor. Aside from the prolongation of life, however, there is

the problem of pain. Bloodgood has found in instances in which one metastatic lesion is present or in which a bone with multiple lesions is easily accessible to surgical measures, and in which the condition of the patient is such as to withstand the operation, that much relief from pain can be given by resection of the affected portion of the bone. One important factor in the treatment of this tumor by irradiation is the extremely resistant character of hypernephroma to low voltage radiation.²⁰ Unless roentgen therapy in keeping with that discussed under carcinoma of the breast is available, the patient should be referred elsewhere for treatment.

TUMORS OF MALE AND FEMALE GENITAL TRACT

Prostate.—Carcinoma of the prostate with metastases to bone is of frequent occurrence, as reported by those clinics and laboratories where considerable genito-urinary material is seen.²¹ From among 1,020 cases of cancer of the prostate in the Brady Urological Institute and 20 cases registered by the Surgical Pathological Laboratory of the Johns Hopkins Hospital, 134 instances of metastases to the bone were found. It must be pointed out, however, that roentgenograms have been made in only about 50 per cent of the total number of cases, and in only 25 per cent of this number were secondary deposits in the bone found.

The bones most frequently involved are the pelvis and vertebrae, particularly the lumbosacral, more rarely the femurs and in two instances the lower end of the tibia and the skull.

The age incidence of the men is well beyond the age of 50 (table 6 A). These men showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted. In a personal communication with Dr. Waters and Dr. Hugh Young's clinic, I am informed that many patients following prostatectomy for extremely small carcinomas, which are actually found on subsequent pathologic examination of the prostate, develop osseous lesions a few years later.

The clinical course of these patients is one of progressive emaciation, secondary anemia and excruciating pains in the affected bones.

Roentgen Studies.—The usual x-ray picture of the bones invaded by the tumor is one of an osteoplastic nature. There is marked increase in formation of the bone, with areas of lighter mottling which suggest some destruction (fig. 26).

20. Dresser, R.: Metastatic Manifestations of Hypernephroma in Bone, *Am. J. Roentgenol.* **13**:342, 1925.

21. Bumpus, H. C.: Roentgen Rays and Radium in the Diagnosis and Treatment of Carcinoma of the Prostate, *Am. J. Roentgenol.* **9**:269, 1922. Blumer, G.: A Report of Two Cases of Osteoplastic Carcinoma of the Prostate with a Review of the Literature, *Bull. Johns Hopkins Hosp.* **20**:200, 1909.

TABLE 6.—*Malignant Disease of the Male Genital Tract with Metastases to Bone*

A. Carcinoma of the Prostate										
B.U.I.* No.	Race	Sex	Age	Location of Metastases	Appearance of Symptoms Attending Metastases	Treatment of Primary Tumor†	Roentgenogram	Duration of Primary Tumor Before Treatment and Metastases, Mo.	Interval Between Primary Tumor and Metastases, Mo.	Result
19677	W	M	59	Right ischium	X-rays, radium, March, 1930	Suggestive of metastases	24	26	Dead 23 days after operation
19508	W	M	78	Pelvis and spine	Pain	P.P., May, 1913	Positive for metastases	12	..	
19523	W	M	59	Spine	X-rays	Suggestive of metastases	72	..	
19453	W	M	62	Right ischium	X-rays, radium, April, 1930	Positive for metastases	72	72	
19401	W	M	74	Spine and pelvis	X-rays, radium, March, 1930	Positive for metastases	60	..	
19351	W	M	66	Sacrum	Pain	X-rays	Positive for metastases	6	..	
19264	W	M	70	Pelvis	Pain	X-rays	Positive for metastases	8	..	
19238	W	M	70	Spine, pelvis	X-rays	Positive for metastases	36	36	Dead 1½ mo. later
19219	W	M	70	5th lumbar vertebra	Pain	Probable metastases	24-36	2	Dead less than 1 mo. after observation
19158	W	M	61	Pelvis	X-rays, radium, Jan., 1930	Positive for metastases	12	12	
19102	W	M	64	5th lumbar vertebra and ischium ilium	Pain	Punch operation, Dec., 1921	Positive for metastases	36	36	
18069	W	M	61	Pelvis and lumbar vertebra	Pain	Positive for metastases	12	..	
18889	W	M	60	Ischium	Pain	X-rays	Positive for metastases	12	12	
18822	W	M	60	Lumbar spine	Pain	X-rays, radium, Aug., 1929	Positive for metastases	24	24	
18694	W	M	70	Pelvis, symphysis	X-rays, radium, July, 1929	Positive for metastases	¾	..	
18391	W	M	70	Left ilium	Pain 12 mo. after onset; urinary symptoms	Radium	Suggestive of metastases	18	..	
18138	O	M	68	Sacrum, left ischium, right ilium	P.P., Jan. 1929	Positive for metastases ?	4	..	
18119	W	M	66	Right ischium, left ilium	Conservative P.P., Jan. 1929	Positive for metastases	24	..	
18085	W	M	..	Spine, pelvis	X-rays, radium, Dec., 1928	Positive for metastases	22	..	Alive 6 mo. after treatment
18017	W	M	59	Sacro-iliac region	Pain	Radium, x-rays, 1928	Positive for metastases	4	..	
18011	W	M	50	Lumbar vertebra, symphysis pubis	Pain	Radium, Nov., 1928; x-rays	Suggestive of metastases	36-48	1	
17993	W	M	63	Vertebra, occiput, ribs (autopsy)	Headache?	Cystotomy, Nov., 1928	No roentgenogram; metastases found at autopsy	5	..	Dead following operation
17874	W	M	60	2d lumbar vertebra	Radium, colostomy, 1929	Positive for metastases	6	..	
17841	W	M	61	Pelvis	Pain	P.P., Jan., 1930	Positive for metastases	12	..	
17836	W	M	50	Left ilium	P.P., Oct., 1928	Suggestive of metastases	12	..	
17610	W	M	47	Seminal vesicle	Pain	Radium, April, 1927; x-rays	Positive for metastases	12	..	
17472	W	M	71	Left ilium	Pain	P.P., June, 1928	Suggestive of metastases	24	..	
17461	W	M	56	Spine, pelvis	X-rays, conservative	Positive for metastases	21-36	21-36	
17387	W	M	53	Pelvis, sacrum	Pain	X-rays	Positive for metastases	48	48	
17391	W	M	66	Spine, pelvis	X-rays, radium, June, 1928	Positive for metastases	27	27	

17381	W	M	67	4th lumbar vertebra	Pain	X-rays (no date given)	Suggestive of metastases	12	14
17303	W	M	76	Spine, 4th and 5th lumbar vertebrae	X-rays, conservative; P.P., April 1, 1928	Positive for metastases	3	4
17195	W	M	65	Right ilium	Radium, March, 1928	Suggestive of metastases	8	..
17179	W	M	60	Spine, pelvis	S.P., 1909; X-rays	Positive for metastases
17168	W	M	85	Pelvis	Radium, 1928	Positive for metastases	26	..
16922	W	M	72	Pelvis, skull	Pain	P.P., Jan., 1928	Positive for metastases	13	..
16802	W	M	62	Pelvis, spine	Pain	Radium, Dec., 1927; X-rays	Positive for metastases	8	..
16765	W	M	62	Lumbar vertebra and pelvis	Punch operation, Nov., 1927	Positive for metastases	1	..
16499	G	M	80	Lumbar vertebra and pelvis	P.P., Sept., 1927	Positive for metastases	10	..
16451	W	M	67	1st, 2d and 3th lumbar vertebrae	P.P., conservative, Aug., 1927	Positive for metastases	12	15
16419	W	M	60	2d lumbar vertebra	Pain	P.P., conservative, Aug. 1927; X-rays, Oct., 1927	Positive for metastases	6	..
16252	W	M	57	Symphysis pubis	Excision of tumor, March, 1927; postoperative radium and conservative P.P., July, 1927	Positive for metastases	9	14
16091	W	M	55	Lumbar vertebra	Pain	P.P., conservative, June, 1927; X-rays	Positive for metastases	12	..
16027	W	M	55	Right ilium, ischium, 5th lumbar vertebra	Pain	P.P., Aug., 1927; X-rays and radium, 2 years before	Positive for metastases	24	..
15832	W	M	63	Lumbar vertebra and ilia	X-rays, radium, May, 1925	Positive for metastases	12	10
15794	W	M	71	5th lumbar vertebra, sacrum, right ilium	P.P., April, 1927; radium	Suggestive of metastases	60	..
15791	W	M	70	Lumbar vertebra, sacrum	Pain	X-rays, radium, March, 1927	Suggestive of metastases	12	6
15761	W	M	56	Pelvis, sacrum, coccyx	Pain	P.P., March, 1927	Strongly suggestive of metastases	21	12
15647	W	M	61	Ilium, ischium, pubis	Sciatic pain	P.P., March, 1927	Positive for metastases	60	..
15529	W	M	72	Pelvis	Pain	Radium, X-rays, 1926	Positive for metastases	36	..
15504	W	M	66	Ischium, sacrum, lumbar spine	Pain	X-rays, Feb., 1927	Positive for metastases	7	..
15476	W	M	82	Spine, pelvis	Pain	P.P., Dec., 1926; X-rays	Positive for metastases	4	..
15470	W	M	75	Symphysis pubis	P.P., conservative, Oct., 1926	Positive for metastases	8	..
15371	W	M	80	4th lumbar vertebra, sacrum, ilium	Suggestive of metastases	18	..
15377	W	M	63	Pelvis	P.P., May, 1926	Positive for metastases	21	..
15346	W	M	..	Pelvis	Pain	P.P., conservative, Nov., 1926	Suggestive of metastases	36	..
15275	W	M	..	Pelvis	P.P., Sept., 1926	Positive for metastases	12	..
15241	W	M	..	Spine, pelvis	P.P., Oct. 1926	Positive for metastases	18	..
15154	W	M	66	Spine, pelvis, right and left scia	Radium advised	Positive for metastases	1	..
14614	W	M	71	Sacrum, 5th lumbar vertebra	Pain	P.P., April, 1926	Suggestive of metastases	9	..
14598	W	M	68	Sacro-iliac region	Radium, April, 1926	Probable metastases	18	21
14485	W	M	46	Right ilium	P.P., conservative, April, 1926	Suggestive of metastases	22	14
14413	W	M	61	Pelvis	Radium, X-ray, Feb., 1926	Positive for metastases	21	..
14423	W	M	69	Sacrum, ilium, right ischium	X-rays, Dec., 1925	Positive for metastases	18	..

* Brady Urological Institute.

† In this column P.P. indicates perineal prostatectomy; S.P., suprapubic prostatectomy.

TABLE 6.—Malignant Disease of the Male Genital Tract with Metastases to Bone—Continued

B.U.I. No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Röntgenogram	Duration of Primary Tumor Before Treatment and Metastases, Mo.	Interval Between Primary and Metastases, Mo.	Result
14192	W	M	65	Sacrum, ilia	Pain	P.P., 1922	Positive for metastases	36	18	
14140	W	M	65	Left ilium, symphysis pubis, sacrum	Pain	Radium, x-rays, Sept., 1925	Very suggestive of metastases	25	18	
13936	W	M	74	Ischium, right pubis, 2d lumbar vert.	Pain	Radium, x-rays, Sept., 1925	Positive for metastases	12	..	
13913	W	M	78	Sacrum, ilium, pubes	Pain	Radium x-rays, Sept., 1924; radium July, 1925	Positive for metastases	6	..	
13767	W	M	69	Sacrum, ilium, lower lumbar vertebrae	Pain	Radium, July, 1925	Positive for metastases	24	..	
13925	W	M	77	Ilii	Pain	Radium, July, 1925	Very suggestive of metastases	48	..	
13171	W	M	56	5th lumbar vertebra, sacrum, ilium, left pubis	Pain	Cystotomy, Nov., 1924	Positive for metastases	12	..	
13466	W	M	72	Pelvis	Pain	Positive for metastases	24	..	Dead few mo. later
13394	W	M	52	Right ischium	Pain	Radium, April, 1925	Positive for metastases	15	..	
13356	..	M	..	Pelvis, upper end of right femur	Positive for metastases	
13317	W	M	78	Pelvis, sacrum	Positive for metastases	21	..	Dead before treatment was begun
13311	W	M	77	Pelvis	P.P., March, 1925	Suggestive of metastases	24	..	Dead from operation
12993	W	M	57	Pelvis	Pain	Positive for metastases	
12757	W	M	75	Right ilium	Radium, Sept., 1924	Probable metastases	3	1	
12859	W	M	71	Pelvis, lumbar vertebra	Pain	X-rays, radium, Oct., 1924	Positive for metastases	9	..	
12580	W	M	68	5th lumbar vertebra	Pain	X-rays, radium, March, 1924; P.P., Jan., 1925	Beginning metastases	
12553	W	M	64	Right ilium	Pathologic fracture	X-rays	Positive for metastases	9	..	
12511	W	M	66	Ischium, right pubis	Pain	P.P., June, 1924; postoperative x-rays	Positive for metastases	12	..	
12405	W	M	64	Spine, pelvis, sacrum	Pain	Radium, June, 1924	Positive for metastases	108	..	
12188	C	M	57	Pelvis, lower lumbar vertebrae	Pain	X-rays, radium, Jan., 1924; P.P., July, 1924	Positive for metastases	24-36	..	
12159	W	M	63	Spine, pelvis	Pain	X-rays, radium, advised	Positive for metastases	6	..	
12275	W	M	70	Pelvis	Stiffness of hip	P.P., May, 1924	Positive for metastases	60	..	
12257	W	M	58	Spine, pelvis	S.P., May, 1923; x-rays and radium	Positive for metastases	48	..	Dead 15 mo. after operation
12081	W	M	60	Symphysis pubis, left femur, right ilium	Punch operation and radium, Feb., 1924; conservative P.P., March, 1924	Suggestive of metastases	12	2	
12060	W	M	63	Lumbar vertebrae, sacrum, ribs	Pain	P.P., radium, Feb., 1924	Positive for metastases	9	..	
12055	W	M	50	Pain	X-rays, 1925	Sclerosis of vertebrae and bones of pelvis; no definite metastases	

11901	W	M	58	Sacrum, ilia	Pain	X-rays, Nov., 1923	Positive for metastases	5	..	
11882	W	M	58	3d lumbar vertebra, sacrum, ilia	Pain	Radium, x-rays, 1921-1923	Positive for metastases	24	..	
11825	W	M	68	5th lumbar vertebra, right ilium,	Pain	Positive for metastases	6	..	
11778	W	M	63	pubes, sacrum	Paraplegia	S.P., 1923	Positive for metastases	6	..	Dead (?)
11650	W	M	66	Pelvis, spine, 4th and 5th lumbar vertebrae	X-rays, Aug., 1923	Positive for metastases	
11575	W	M	63	Sacro-iliac region, right	Radium, July, 1923	Suggestive of metastases	12	..	Dead 3 weeks after treatment
11552	W	M	74	Pelvis, sacrum	Pain	Radium, July, 1923	Positive for metastases	26	..	
11467	W	M	63	Sacrum, pelvis	Radium, June, 1923	Positive for metastases	30-18	..	
11419	W	M	57	Sacrum, spine	Pain	Radium, June, 1923	Positive for metastases	60	2	
11388	W	M	69	Pelvis, lower lumbar vertebrae	Pain	Radium, April, 1923; x-rays, May, 1923	Positive for metastases	12	..	
11244	W	M	48	Spine, pelvis	Pain	P.P., x-rays, March, 1923	Suggestive of metastases	4	..	Dead 2 mo. after appearance of metastases
10938	W	M	75	Ribs, vertebrae	Pain	Punch operation after radium and x-rays, Dec., 1921	X-ray negative; autopsy findings; extensive metastases	21	24	
10919	W	M	75	Sacrum	Radium, Nov., 1922	Positive for metastases	24	..	Living 2½ yr. later
10776	W	M	64	Right ilium	Pain	P.P., conservative; radium, Sept., 1922	Positive for metastases	12	9	
10657	W	M	59	Spine, pelvis, sacrum	Pain	Radium, July, 1922; x-rays S.P., x-rays, radium, 1922 (June-July)	Positive for metastases	1¼	..	Dead 1 mo. after x-ray treatment
10562	W	M	75	Femora, pelvis, spine, humerus, clavicles, scapulae	Pain	Radium, June, 1922	Suggestive of metastases	2	..	Dead
10517	W	M	76	Pelvis	P.P., March, 1922	Positive for metastases	12	..	
10495	W	M	70	Symphysis pubis, right hip	Pain	P.P., radium, May, 1922	Positive for metastases	12	..	Dead 7 mo. after operation
10491	F	M	67	Sacrum, ilia, 11th dorsal vertebra	P.P., radium, May, 1922	Positive for metastases	18	..	Dead 11 mo. after operation
10478	W	M	71	Sacrum, pelvis	P.P., May, 1922; radium, May, 1922	Positive for metastases	
10460	W	M	75	Lower lumbar vertebrae	P.P., Feb., 1922, radium 2 weeks later (S.P., 10 months before)	Positive for metastases	
10391	W	M	76	Spine	P.P., April, 1922	Suggestive of metastases	1	..	
10655	W	M	59	4th and 5th lumbar vertebrae	Pain	Radium, Nov., 1921	Positive for metastases	15	..	
9958	W	M	78	4th and 5th lumbar vertebrae	Pain	Radium	Positive for metastases	2½	..	
9493	W	M	64	vertebrae, pelvis	Pain	P.P., March, 1921	Positive for metastases	40	33	
9700	W	M	51	Left ilium, sacrum	Radium and x-rays	Suggestive of metastases	36	..	
9018	W	M	68	Sacrum	Pain	P.P., Oct., 1920	10	1	
8493	W	M	62	Spine, pelvis	Pain	Radium, Feb.-March, 1920	Positive for metastases	Dead 6 mo. after initiation of treatment
8372	W	M	70	Pelvis	Pain	P.P., Dec., 1919; radium, Jan., 1920; x-rays	Positive for metastases	12	6	Dead 15 mo. after appearance of metastases
8234	W	M	62	Spine, pelvis	P.P., Dec., 1919	Positive for metastases	132	51	Dead 2½ yr. after appearance of metastases
7272	W	M	69	Pain	P.P., Nov., 1918	Negative for metastases	Dead 1 yr. after operation

TABLE 6.—*Malignant Disease of the Male Genital Tract with Metastases to Bone—Continued*

B.U.I. No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor		Result
								Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	
7240	W	M	61	Sacrum, coccyx	Pain	P.P., 1918	Positive for metastases Strongly suggestive of metastases	36	..	Dead 1½ yr. after operation
6838	W	M	66	Sacrum	Pain	P.P., 1918	Positive for metastases	
6745	W	M	71	4th and 5th lumbar vertebrae, sacrum, ilia	Pain, 3 yr.; incontinence of urine and feces	P.P., 1918; radium		
6108	W	M	79	Lumbar vertebrae	Suggestive of metastases	144	108	Dead 9 yr. after operation
4417	W	M	68	Lumbar vertebrae, and pelvis	S.P., 1915; radium and X-rays	Positive for metastases	120	..	
2131	W	M	57	5th lumbar vertebra, sacrum, ilium	Pain	P.P., 1909; punch operation, 1924; excision, 1927	Positive for metastases			
Cases From the Files of the Surgical Pathological Laboratory										
42182	W	M	55	Pelvis	S.P., May, 1929	Positive for metastases	24	..	Dead few months after treatment
33307	W	M	68	Pelvis	X-rays, 1923	Positive for metastases	Dead following operation
18375	W	M	57	Lower end of femur	Pathologic fracture	Amputation of leg, metastases, Oct., 1915	Positive for metastases	6	..	Dead a few days after observation
10341	W	M	51	Upper third of femur	Pain, pathologic fracture	Positive for metastases	Dead 8 mo. after operation
1643	W	M	75	Tibia, shaft	Swelling	Amputation of thigh (metastatic growth), Jan., 1897	10	3	
B. Testicular Malignant Disease										
Path. No.	Race	Sex	Age	Primary Tumor	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Duration of Primary Tumor		Result
								Before Metastases, Mo.	Interval Between Primary Treatment and Metastases, Mo.	
42856	W	M	56	Sarcoma of testicle	Skull, frontal bone	Tumor	Excision of right testicle, April, 1930	Roentgenogram Positive for metastases	8	Dead 3 mo. after operation Well 3 yr., 9 mo. before after operation
29069	W	M	40	Carcinoma of testicle	Ribs, 4th and 5th	Pain	Orchiectomy, Feb., 1922; postoperative radium	Positive for metastases	2	Metastases observed in x-ray 3 mo. before symptoms of primary tumor

* Duration of metastatic growth.

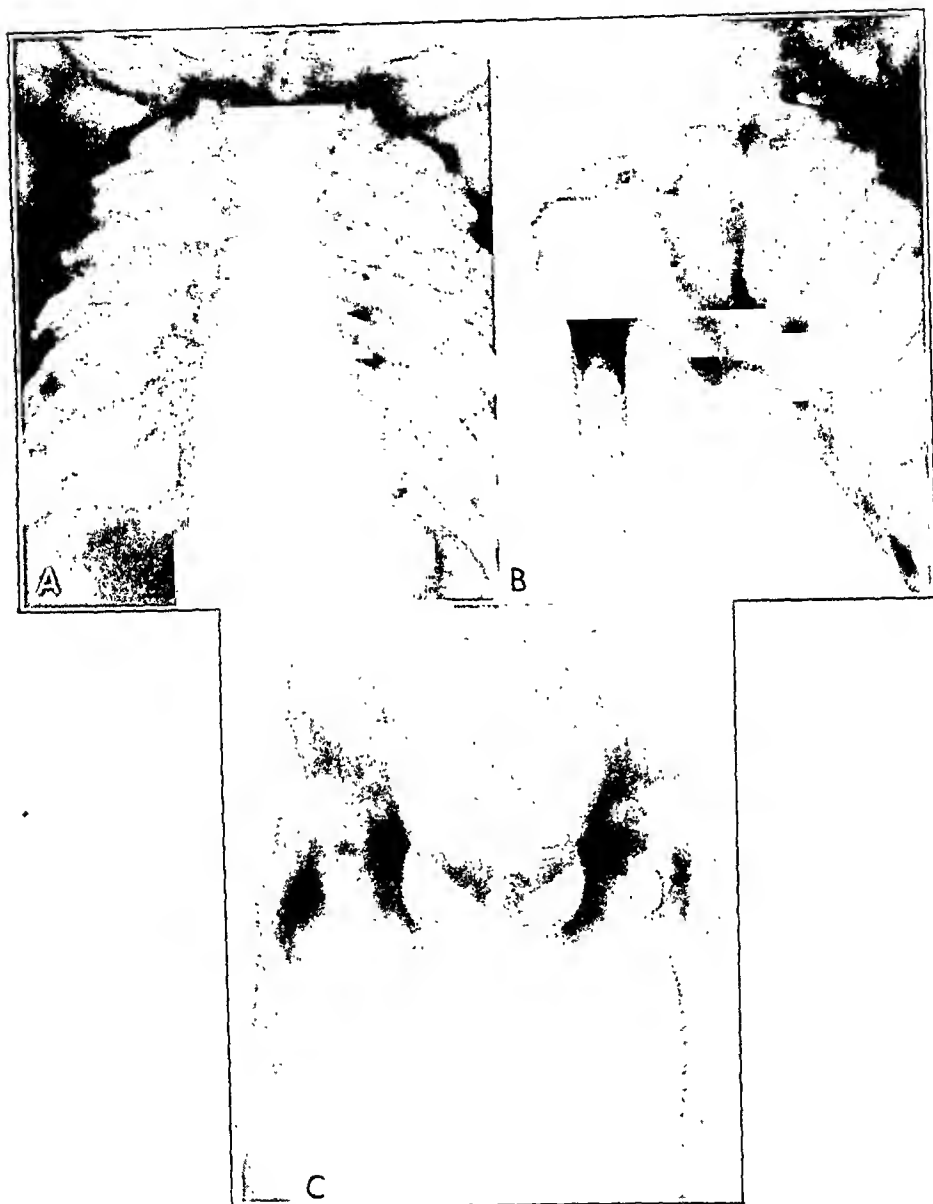


Fig. 26 (path. no. 42182).—Osteoplastic nature of bony metastases from carcinoma of the prostate as depicted in the roentgenogram. *A* shows involvement of the ribs and clavicle with some bony destruction and formation of new bone. *B*, the upper end of the humerus with marked sclerosing reaction in the region of the head from tumor invasion. *C*, shows multiple involvement of the entire pelvis and associated involvement in the upper part of both femurs. Note again the marked production of bone in the affected areas.

Simpson²² has reported a case in which there was no clinical roentgenographic or gross anatomic evidence of vertebral metastases, which on subsequent microscopic study, revealed generalized medullary carcinoma of the prostate gland.

Bumpus,²³ in a study of 362 cases at the Mayo Clinic, found that the osteoplastic type of bony metastases was by far the more common, but that osteoclastic changes did occur in a few of the cases.

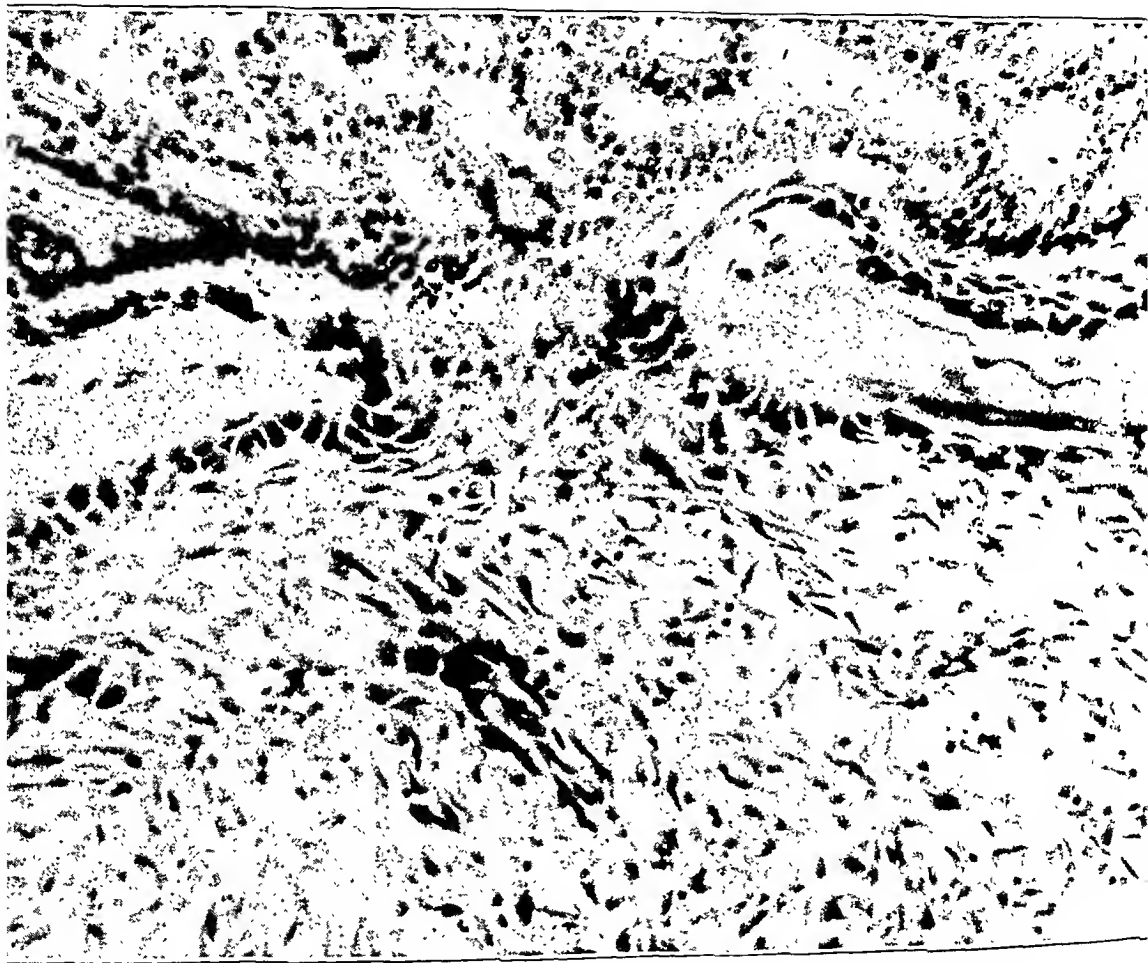


Fig. 27 (path. no. 1643).—Photomicrograph showing definite glandular structure of the invading prostatic cancer, while about this tumor tissue reactive bone can be seen which is an attempt on the part of the osseous structure to wall off the advance of the tumor.

On gross examination, these metastatic areas are usually white or grayish nodules with many newly-formed trabeculae of bone as well

22. Simpson, W. M.: Diffuse Vertebral Metastasis of Prostatic Carcinoma Without Bony Changes, *Am. J. Roentgenol.* **15**:534, 1926.

23. Bumpus, H. C., Jr.: Carcinoma of the Prostate, *Surg. Gynec. & Obst.* **32**: 31, 1921.

as spicules of old bone undergoing absorption by direct contact with the tumor cells. The prostatic glandular structure can be made out in many of the secondary deposits in bone. About this tumor tissue is found much reactive bone, which is an attempt on the part of the osseous structure to wall off the disease invading its substance (fig. 27).

The reaction of bone to prostatic carcinoma is quite the reverse of that usually seen in other metastatic lesions, except where osteoclastic invasion by tumor has been treated by roentgen therapy. Many possibilities arise in connection with this phenomenon. The most tenable one, however, is that the invasive powers of the metastatic tumor are so moderate that proliferation of the bone can keep pace with the invasion by tumor. The validity of this statement becomes more apparent when one considers the reaction of tumor deposits from other primary lesions to roentgen therapy.

Roentgen therapy offers some relief from pain but is not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection of the affected bone or amputation of the diseased limb has in some instances made the patient more comfortable for the time he had to live.

Testicle.—Malignant disease of the testicle with metastases to bone is of rare occurrence. Of thirteen cases in which the diagnosis was carcinoma, in only one instance is there a record of metastases (table 6 B).

A man, aged 40 (path. no. 29669), had orchitis of the left testicle with subsequent atrophy at the age of 18, after an attack of measles. For two months prior to admission to the hospital twenty-two years later, he had noted a swelling in the testicle. On examination, it was found to be a hard, irregular mass. There was no enlargement of the regional lymph glands and no palpable mass in the abdomen. The blood and urine were normal. On roentgen examination of the various bones, the fourth and fifth ribs showed destruction. The patient had noted some pain in the region of these lesions for over a year. Just prior to admission, there had been a noticeable loss of weight. Following roentgen therapy both over the testicle and the affected ribs, orchectomy was performed, and uneventful recovery followed. In 1922, the patient had remained well twenty-eight months with recalcification of the fourth and fifth ribs. Since that time, the patient has been lost from observation.

In forty-two cases of sarcoma of the testicle registered in the Surgical Pathological Laboratory, there is only one instance of metastases to the bone (table 6 B, path. no. 42856).

A white man, aged 56, presented himself with a growth on his forehead of eleven months' duration. When first noticed, it was the size of the index finger. There had been no pain or headache. A swelling of the right testicle had been noticed for at least a year and a half which followed a slight injury. Six months prior to his admission to the hospital, the swelling suddenly disappeared with

subsequent fluctuations in size. Seven weeks before, the patient had what he called an attack of influenza, with a temperature of 102 F. Following this, a physician was interviewed who gave the patient serum treatment for the tumors, which was followed again by an elevation of temperature. On examination, the tumor in the forehead was found to be the size of a small orange and extended from the nose to the hair line. There was fluctuation in the tumor.

The x-ray picture revealed destruction of the frontal bone, particularly of the outer table, immediately above the frontal sinuses with infiltration and swelling of the overlying soft structures. There was no evidence of metastases in the other

TABLE 7.—*Maglinant Disease of the Female Genito-Urinary with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
<i>Carcinoma of the Female Genital Tract</i>								
40714	W	F	53	Carcinoma of uterus	Right femur, right pelvis
3779	W	F	35	Carcinoma of uterus	Right ilium	Exploration, drainage	Lived 10 mo.
3429	C	F	49	Carcinoma of uterus	Right pelvis (ilium)	Lived 4 mo.
36552	W	F	60	Carcinoma of cervix	Right humerus, right side of skull, upper third of femur
20111	W	F	38	Carcinoma of cervix	Ilium
27170	W	F	47	Carcinoma of ovary	Metacarpal, right foot
<i>Carcinoma of the Bladder</i>								
11970	W	F	50	Carcinoma of bladder	Tibia, right	Resection of tibia
<i>Sarcoma of the Female Genital Tract</i>								
29529	W	F	14	Sarcoma of ovary	Skull, lower third of left femur, upper end of femur, left ilium	X-rays	Lived 13 mo.

bones of the skeleton. The testicle was removed by Dr. Bloodgood, and the patient was given roentgen therapy, with rapid disappearance of the tumor in the forehead, which was soon followed, however, by vomiting and other systemic disturbances. There was never severe anemia or emaciation. The patient died three months after operation, having lived fourteen months from the first sign of the metastases.

Bladder.—One example of carcinoma of the bladder with metastases to bone (table 7, path. no. 11970) is recorded.

A white woman, 50 years old, six weeks before admission to the hospital felt pain in the inner portion of the right tibia on walking. This was followed by swelling of the right foot. The pain was worse at night, and marked swelling developed in the midshaft of the tibia. On roentgen examination, there was

evidence of destruction of the bone beneath the periosteum on the side toward the fibula, with slight evidence of formation of new bone, characteristic of metastatic cancer. Resection of the tibia was performed, and microscopic examination revealed tissue of the transitional type resembling that seen in tumors of the bladder.

Following the operation, hematuria developed, and after two months and nine days a cystoscopic examination was done which showed a tumor of the bladder in the region of the trigone. Unfortunately, the patient was lost from observation soon after recovery from operation, so that the ultimate progress of the disease could not be ascertained.

Uterus.—From among eighty-six cases with carcinoma of the uterus, five cases (5.6 per cent) showed metastases to bone (table 7), two of these patients having the primary lesion located in the cervix. The age incidence in these cases extended from 35 to 60 years. The metastases were found four times in the pelvis, twice in the femur and once in the humerus, skull and metacarpals of the right foot.

Clinically, varying degrees of pain with disturbances of use in the affected extremities were common symptoms. At times an associated swelling was noted in the glands of the groin and of the affected limb.

Owing to the fact that uterine carcinoma as a whole invades lymph nodes relatively late, Ewing²⁴ has found a striking tendency of the disease to remain localized either to the uterus or to its immediate vicinity. As a rule, tumors of the fundus long remain confined by the muscular wall. This is not the case in cervical carcinoma, which invades the parametrium early. The duration and type of the disease undoubtedly influences the rapidity of the extension.

The clinical course of the advancing disease is dominated by secondary invasion of surrounding organs, many cases terminating through uremia from occlusion of the ureters. Characteristic cachexia develops in most cases, but nutrition may remain surprisingly good.

The x-ray picture shows destruction of the bone (fig. 28). There is little tendency to formation of bone, and there is nothing typical of the lesion to set it apart from the other osteoclastic types of metastases.

In this group of cases there is little to offer with regard to treatment except the general principles that have been laid down in the preceding pages. Ford²⁵ recently showed that there is a slightly smaller percentage of cases showing distant metastases, including metastases to the bone, following adequate irradiation of the primary lesion than in those cases in which radium therapy is not employed. Some relief from pain

24. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 601.

25. Ford, F. A.: *Distant Metastases in Carcinoma of the Cervix of the Uterus*, *Minnesota Med.* **13**:489 (July) 1930.

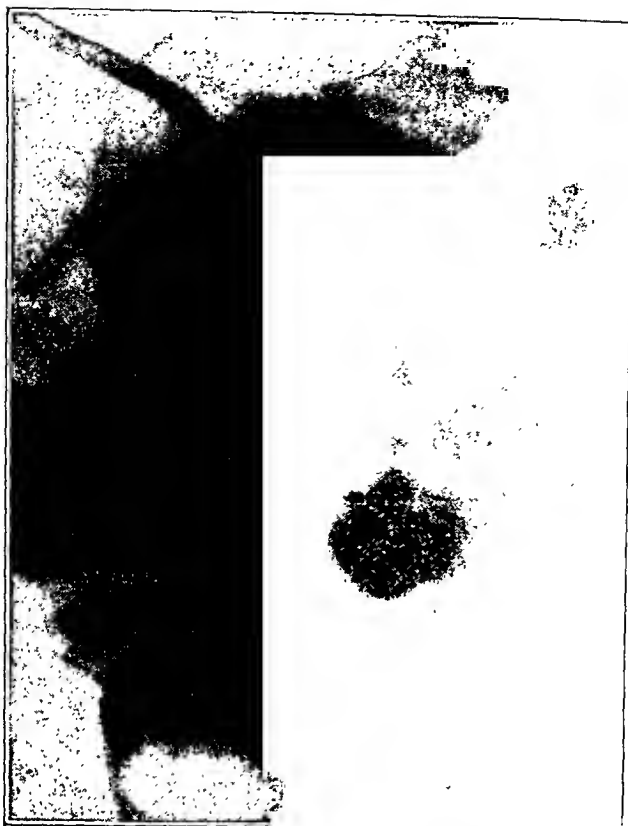


Fig. 28.—Roentgenogram of the pelvic bones showing invasion of the ilium by extension of tumor from the uterus.



Fig. 29 (path. no. 29529).—Roentgenogram depicting invasion of the tumor at the lower end of a femur from an ovarian sarcoma. Note the destruction of the bone and subperiosteal involvement on the posterior aspect of the bone.

in the osseous lesions is obtained by irradiation, but this is more transient than the relief following the irradiation of mammary carcinomatous metastases to bone.

Ovary.—There are two instances, 2.8 per cent, of ovarian tumor with metastases to bone among sixty-nine such cases in this laboratory (table 7).

One of these patients was a woman, aged 47 (path. no. 27170), in whom, four months prior to admission, sudden pain developed over the entire abdomen, and lasted for a few days. The abdomen soon became filled with fluid; a subsequent laparotomy was performed, and bloody fluid was found. The right ovary was much enlarged. The patient made an uneventful recovery and returned home. Twelve months ago, she began to limp because of discomfort in the right foot. A roentgenogram of the foot showed destruction at the proximal end of the third metatarsal bone. Roentgen therapy was administered, and the condition of the foot improved. The patient has been lost from observation.

The other case (path. no. 29529) was that of a young girl, aged 14, who first noticed pain in the left knee with limp, and pains in the abdomen with some diarrhea. Eight months later, a lump appeared on the posterior portion of the skull. A laparotomy was subsequently done for pain in the abdomen, free fluid was found, and a small tumor of the right ovary was removed and was diagnosed sarcoma (mesothelioma).

Roentgen therapy was instituted, and though some relief from pain followed, the course was progressively downward. The patient died twenty months after the first symptoms of metastases. Roentgen examination revealed areas of destruction in the skull and in the lower third and the upper end of the femur (fig. 29) and in the left ilium.

MALIGNANT DISEASE OF THE THYROID

In those reports that deal with a large series of cases of malignant disease of the thyroid, metastases to bone are of frequent occurrence. Ehrhardt²⁶ found bones affected in 66 of 238 cases of carcinoma of the thyroid, and Ewing²⁷ is of the opinion that in malignant conditions of the thyroid the bones are involved only less frequently than in cases of mammary and prostatic cancer, giving the following order of frequency in bones affected: skull, sternum, spine, ribs, humerus, femur and pelvis. The metastatic growths appear near the epiphyses either as central (fig. 30) or subperiosteal lesions. Much has been written concerning the so-called metastatic tendencies of the "benign metastasizing goiters." Simpson²⁸ reported three cases in which the

27. Ewing, J.: *Neoplastic Diseases*, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 955.

28. Simpson, W. M.: *Three Cases of Thyroid Metastasis to Bones*, Surg. Gynec. & Obst. 42:489, 1926.

TABLE 8.—*Malignant Condition of the Thyroid with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
40950	W	F	51	Carcinoma of thyroid	Upper end of left humerus	Exploration
40892	..	M	56	Sarcoma of thyroid	Bone	X-rays	Lived 16 mo.
37300	W	F	55	Carcinoma of thyroid	Skull
31358	W	M	70	Carcinoma of thyroid	Ribs and sternum, right 6th 7th and 8th ribs	Lived 24 mo.
28366	W	M	45	Carcinoma of thyroid	Neck of femur	Femur	Curetting of tumor
26823	W	F	54	Carcinoma of thyroid	Upper third of right humerus, right clavicle	Right clavicle	Erysipelas and prodigious toxins (Coley's), radium, amputation and x-rays	Lived 24 mo.



Fig. 30 (path. no. 26823).—Roentgenogram depicting involvement of the bone in the upper end of a humerus. Note the marked destruction and expansion in the region of the nutrient vessels. There is also evidence of diffuse involvement of the lower portion of the shaft without distortion.

microscopic picture of the tissue removed from osseous deposits was that of typical thyroid tissue with the patients apparently presenting clinically benign goiters, but on careful observation of the clinical course and subsequent pathologic changes, these cases were found to show malignant degeneration in the thyroid gland. This, together with evidence which he accumulated, points to the fact that many such cases show some existent malignant change in the thyroid gland.

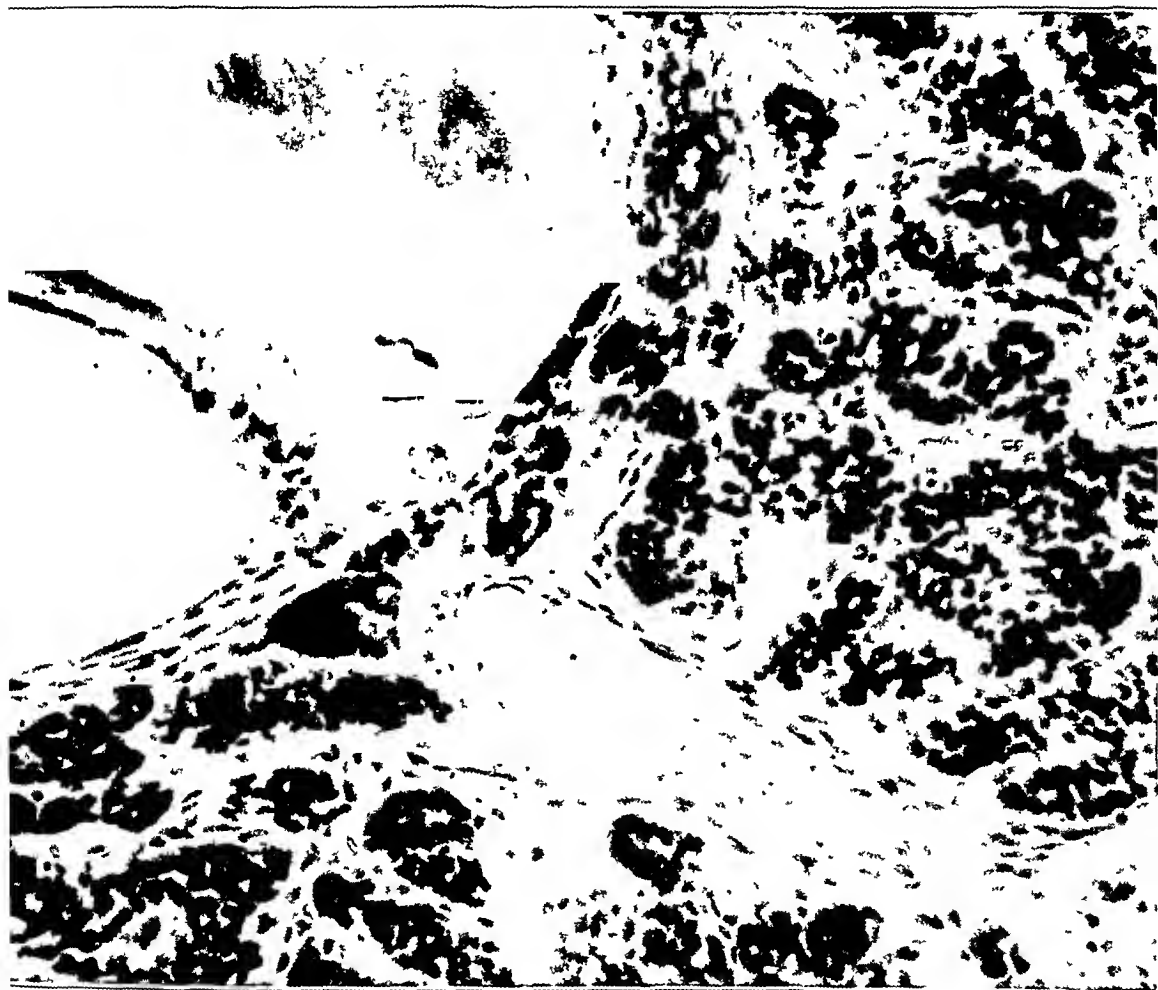


Fig 31 (path no 26823) —Microscopic picture showing marked proliferation of tumor cells, with a spicule of old bone being destroyed by direct contact with the tumor cells.

In the six cases of malignant disease in the thyroid gland, with metastases to bone (table 8) recorded here, the ages ranged beyond 40 and well into late life. The cases were equally divided between the sexes.

There are too few cases to draw any conclusion concerning the incidence of involvement of the bone, but the evidence points to both a lymphatic and a hematogenous type of invasion.

The clinical course in these cases was usually one of progressive emaciation with symptoms referable to the bones that were the seat of the metastases. Pulmonary symptoms where the gland had invaded the structure of the neck and mediastinum causing pressure were marked in some cases.

Roentgen therapy was used in one instance, and in another erysipelas and prodigious toxins (Coley), radium therapy, subsequent amputation and roentgen therapy were combined, but despite the alleviation of pain the course of the disease proved fatal within two years.

The microscopic picture shows marked proliferation of tumor cells with little or no attempt at bone repair. Spicules of old bone are destroyed by direct contact with the tumor cells (fig. 31).

MALIGNANT DISEASE OF THE GASTRO-INTESTINAL TRACT

Stomach.—The literature related to carcinoma of the stomach and its subsequent metastases to bone is limited. Moore,²⁹ of the Mayo Clinic, up to 1919 had not observed a single metastatic lesion to bone from cancer of the stomach. Kaufmann³⁰ reported 2.5 per cent of metastases to bone in a review of 309 cases of malignant disease of the stomach. Schlesingers³⁰ found an incidence of 9.3 per cent in 54 cases, and Jenkinson,³¹ in reviewing the literature, could find only 32 cases in which carcinoma of the stomach had metastasized to bone.

From a series of 537 patients who were found to have carcinoma of the stomach, registered in this laboratory, only 7, or 1.03 per cent, were subsequently found to be affected by metastases to bone (table 9). The ages of these patients ranged between 32 and 71. The bones involved were, in the order of frequency: ribs, 4 cases; pelvis and femur, 3 cases; vertebrae, 2 cases; sternum, skull and scapula, 1 each.

The frequent involvement of the ribs without metastases to the lung points to a lymphatic route of dissemination, while the mode of invasion in more distant bones is open to question.

In one instance (path. no. 39012), a pathologic fracture was found at the lower third of the right femur.

Most of the metastatic lesions in this group were examined at autopsy, but in two instances in which roentgen examinations were recorded (figs. 32 and 33), either diffuse mottling with destruction of bone and no distortion of the bone shell was present, or a slight expansion accompanied the central cystic lesion.

29. Moore (footnote 1, second reference).

30. Quoted by Jenkinson.

31. Jenkinson, E. L.: Primary Carcinoma of the Gastro-Intestinal Tract Accompanied by Bone Metastasis, *Am. J. Roentgenol.* 11:411 (May) 1924.

The clinical course is well illustrated in the following case report (path. no. 43240) :

A white man, aged 40; was admitted to the hospital complaining of an inability to walk, with pain in the legs and in the back of the neck. He had previously suffered for nine months with a sensation of pins and needles in the feet on walking. His feet felt cold and the skin was exceedingly dry over these extremities. Seven months prior to admission, he had fallen on his back, and severe pain had followed for several days. Four months later, a progressive weakness of the legs was noted and finally an inability to walk. Occasionally he had suffered from attacks of vomiting, and there was constant headache.

TABLE 9.—*Carcinoma of the Stomach with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
44477	W	F	54	Carcinoma of stomach	Sternum, vertebra, femur, ribs, pelvis
43240	C	M	32	Carcinoma of stomach	Bones
43244	W	F	70	Carcinoma of stomach	5th left rib
43242	W	M	39	Carcinoma of stomach	Right 4th, 5th and 6th ribs, left 4th, 5th and 9th ribs, 1st lumbar vertebra, 1st and 10th thoracic vertebrae, left parietal bone
43240	W	M	40	Carcinoma of stomach	Right femur and ilium, 2d and 5th right ribs	Rest in bed	Lived 9 mo.
39012	W	M	59	Carcinoma of stomach	Lower third of right femur, left ilium, right acetabulum	Femur	Lived 24 mo. plus
36342	W	M	71	Carcinoma of stomach	Left scapula	X-rays	Lived 14 mo.

On examination, the patient was found to be quite emaciated, and he was unable to sit up in bed; the knee jerks and deep reflexes elsewhere were absent. There was a fulness over the outside of the crest of the right ilium and a distinct thickening of the head of the femur. The blood showed a moderate secondary anemia, which gradually became more severe. The ultimate clinical course was progressively downward, and the patient died nine months after the first symptoms of metastases.

An interesting feature of the blood in cases of metastases of the bone from carcinoma of the stomach is reported by Piney³² and others.³²

32. Parmentier, E., and Chabrol, E.: Anémie grave et métastases cancéreuses dans la moelle des os, Bull. et mém. Soc. méd. d. hôp. de Paris **28**:341, 1909. Schleich, K.: Zur Diagnose von Knochenmarkstumoren aus dem Blutbefunde, Ztschr. f. klin. Med. **59**:261, 1906. Harrington, A. W., and Kennedy, A. M.: Bone Marrow Metastases and Anemia in Gastric Carcinoma, Lancet **1**:378, 1913.



Fig. 32 (path. no. 36342).—Roentgenogram showing diffuse mottling with destruction of the bone in the head of a humerus and in the adjoining scapula from carcinoma of the stomach.



Fig. 33 (path. no. 39012).—Roentgenogram showing diffuse cystic destruction in the lower shaft of a femur from carcinoma of the stomach metastasizing to the bone. In the shaft above the area of destruction the cortex is seen to be eroded from within.

Changes in the blood of a pseudopernicious type were found in these cases, and are recorded in only one other type of metastatic tumor—carcinoma of the breast metastasizing to bone. This is in contrast to the ordinary type of secondary anemia usually seen. In one case of the present series (path. no 44477), a similar condition was noted in the blood.

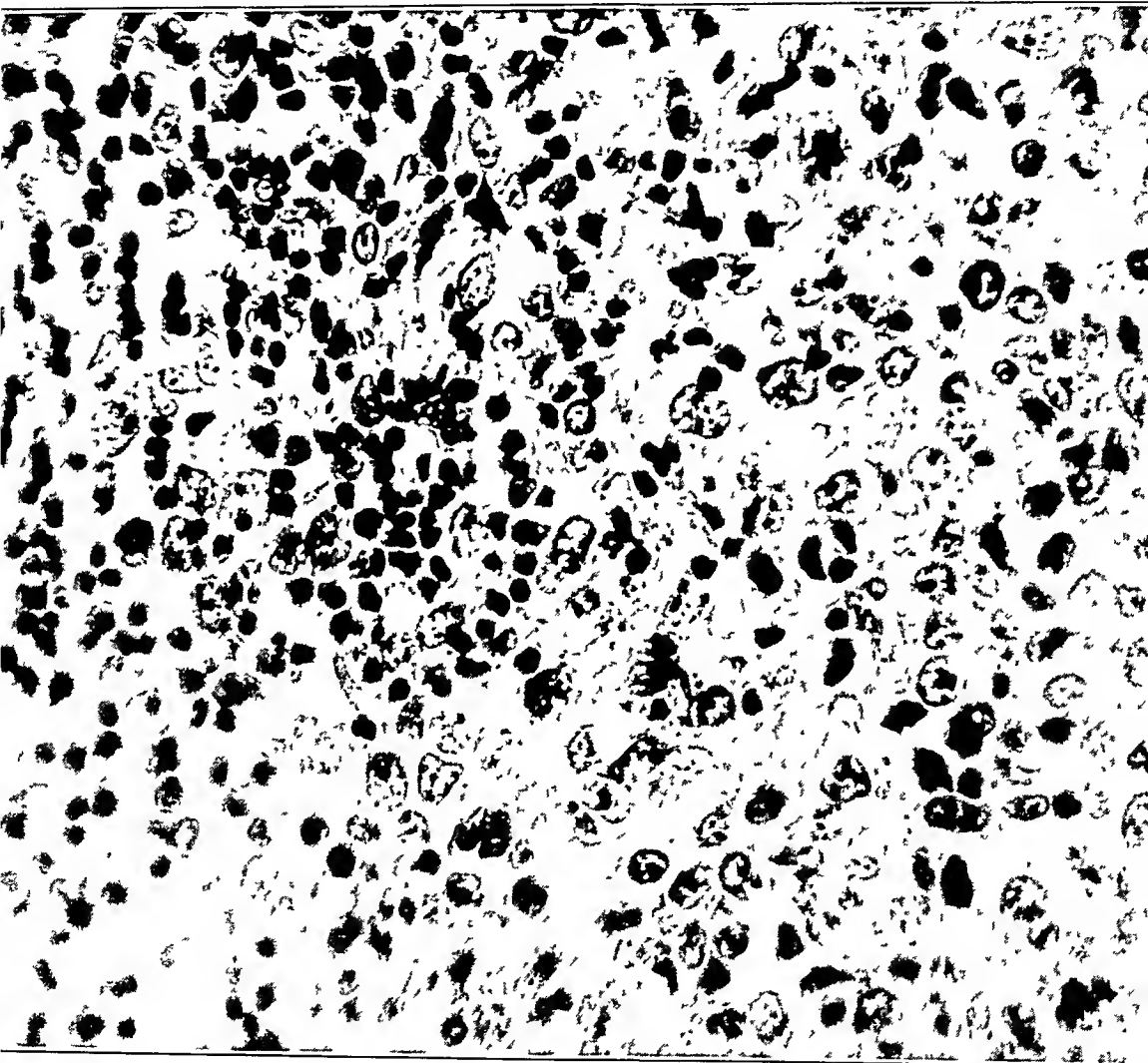


Fig 34 (path no 44477) —Photomicrograph showing invasion of a lymph gland by tumor tissue from medullary carcinoma of the stomach

A white woman, aged 54, had always been healthy until three years before admission to the hospital, when she became quite weak and pale, and began losing weight.

Six months before admission to the hospital she noticed enlargement of all the lymph nodes and a progressive downhill course with fever and sweats. The blood

on admission revealed 3,100,000 red blood cells, 10,600 white blood cells, 340,000 platelets with 30 per cent of polymorphonuclear cells, 6 per cent eosinophils, 2 per cent basophils, 26 per cent myelocytes, 1 per cent myeloblasts, 16 per cent large lymphocytes and 11 per cent small lymphocytes, and also tertian malarial parasites which were present at this examination.

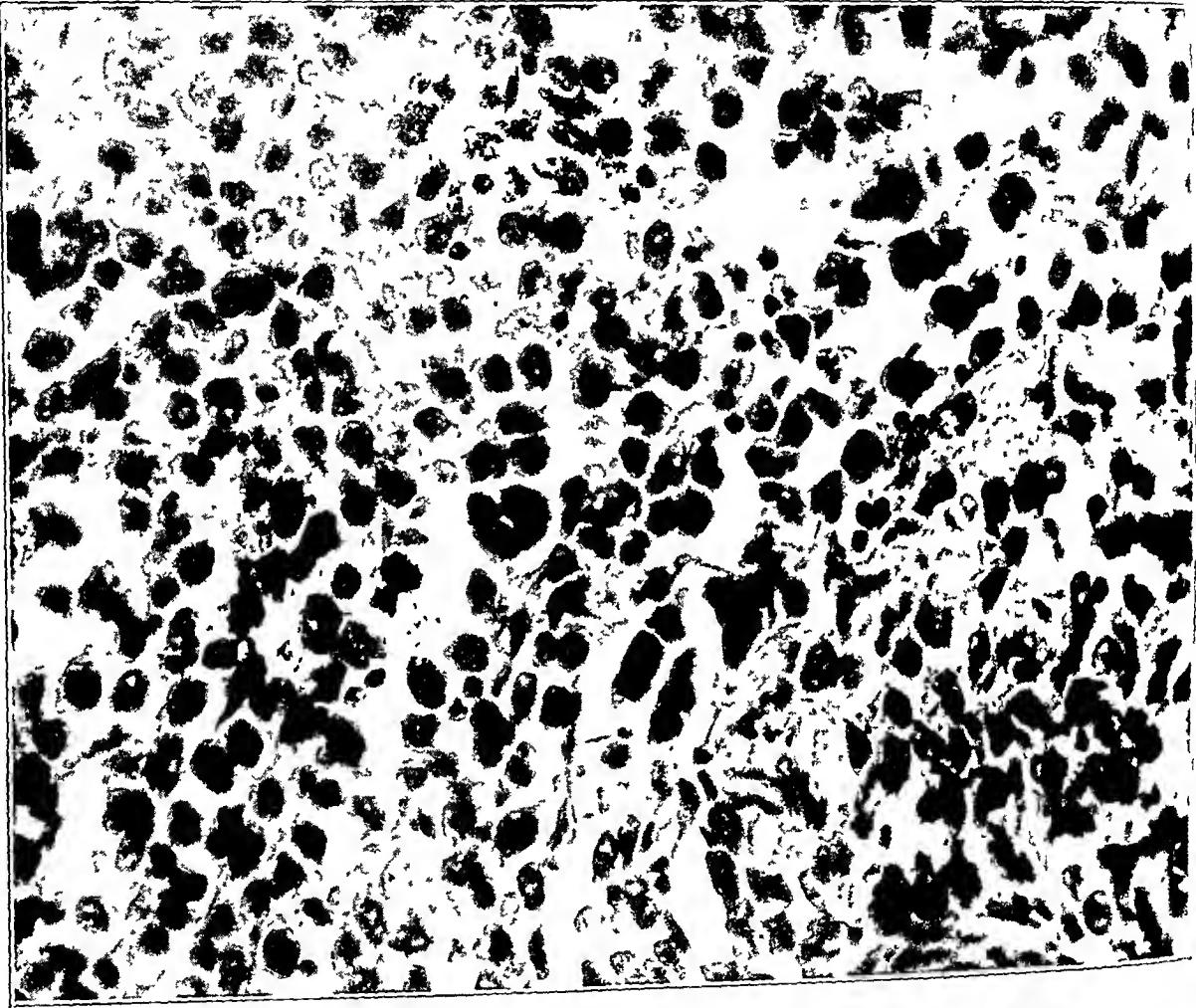


Fig 35 (path. no 44477) —Photomicrograph showing the original primary tumor of medullary carcinoma of the stomach which subsequently metastasized to bone.

A roentgenogram of the chest showed enlarged mediastinal glands, and at this time the long bones were normal. Chemical examination of the blood showed nothing unusual, and a Wassermann reaction was negative.

A lymph gland was removed for diagnosis, and the microscopic picture (fig 34) was thought to be myeloid leukemia.

The further course of the disease was one of progressive emaciation. The anemia became very marked, and fifteen days after admission to the hospital the patient died.

Autopsy was performed, and a large tumor of the stomach with extension to surrounding tissue and mesentery was found. The retroperitoneal, mediastinal, peribronchial, cervical, axillary and inguinal lymph nodes, the spleen, liver and bone (table 9) were involved.

The microscopic picture of the tumor of the stomach (fig. 35) revealed a medullary type of carcinoma.

The bone marrow was diffusely destroyed, and it was easy to distinguish between bone marrow and tumor tissue.

Tumors of other parts of the gastro-intestinal tract occasionally metastasize to the skeletal system, which is represented in the literature by isolated case reports.³³

TABLE 10.—*Malignant Disease of the Gastro-Intestinal Tract with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
Carcinoma of the Gastro-Intestinal Tract								
29861	Carcinoma of esophagus	Lumbar spine
29861½	Carcinoma of cecum	Isehii and pubis
29861¾	Carcinoma of sigmoid	Upper third of right femur
5145	W	F	54	Carcinoma of rectum	Midshaft of right humerus	Humerus	Living after 18 mo., lost from observation
Sarcoma of Gastro-Intestinal Tract								
28258½	W	F	18 mo.	Sarcoma of ileum	Right ilium, left femur right femur, left ilium	Radium	Dead
Primary Carcinoma of the Liver								
25501	C	M	70	Carcinoma	Pelvis, upper end of femur, spine	Lived 6 mo.

Among the primary lesions in this laboratory, single examples of invasion of the bone from malignant conditions of the esophagus, cecum, sigmoid, rectum, ileum and liver are recorded (table 10).

The associated secondary deposits, as in the other primary tumors mentioned, were contributing factors in the ultimate prognosis of these cases. Only one patient in the series was treated by roentgen therapy, with some relief from pain but apparently without prolonging the patient's life.

33. Moon, V. H.: Primary Carcinoma of the Liver with Metastases to Bone, Arch. Path. 8:938 (Dec.) 1919. Brickner, W. M., and Milch, H.: Pathological Fracture of the Humerus due to Carcinoma Metastatic from a "Silent" Growth in the Oesophagus, Internat. Clin. 1:207 (March) 1926. Jenkinson (footnote 31).

CARCINOMA OF THE LUNG

Involvement of the bone was found in four (16 per cent) of twenty-four cases of carcinoma of the lung analyzed in this clinic. Grove and Kramer,³⁴ in a study of twenty-one cases of primary lesions of

TABLE 11.—*Miscellaneous Tumors with Metastases to Bone*

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
Carcinoma of the Lung								
40952	W	M	..	Carcinoma of lung	Lumbar spine, pelvis, skull	X-rays
37838	W	M	39	Carcinoma of lung	Right 9th rib	Resection	Lived 21 mo.
31740	W	M	49	Carcinoma of lung	Ribs, vertebrae	2 ribs
14500	C	F	54	Carcinoma of lung	Skull	Excision of frontal bone
Melanomas								
32176	W	M	44	Melanoma	Middle third of left humerus	Middle third of humerus	Amputation of left arm	Living 7 yr., 6 mo.
10764	W	F	79	Melanoma	Upper third of tibia	Lived 36 mo.
9717	W	M	70	Melanoma	Ribs, clavicle, radius
Nasopharyngeal Tumor								
40299	W	M	67	Adenoid cystic basal cell carcinoma	Skull, jaw, cervical vertebrae, clavicles, scapulae, all ribs, other bones	Excision of nasal polyp, with radium	Lived approximately 36 mo.
Epithelioma of Ear and Heel								
32025	W	F	40	Epithelioma	Lower end of femur	Cauterization of lower end of femur, erysipelas and prodigious toxins (Coley's)
30831	W	M	..	Epithelioma	Malar bone	X-rays, radium	Lived 30 yr. plus
Sarcoma of the Soft Part								
26686	W	M	32	Sarcoma of neck	Clavicle, lower right jaw, tibia	X-rays, erysipelas and prodigious toxins (Coley's)	Lived 24 mo. plus
26683	W	M	33	Sarcoma of neck	Right clavicle, ilium, radius, left tibia, ankle	X-rays

the lung, found 38 per cent metastasizing to bone. A wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull (table 11). Pathologic fracture was found in the ribs of one case at examination.

34. Grove, J. S., and Kramer, S. E.: Primary Carcinoma of the Lung, *Am. J. M. Sc.* 171:250 (Feb.) 1926.

The clinical course of the disease revealed nothing different from that recorded in other metastatic lesions. The x-ray picture shows destruction of the bone with slight formation of new bone, often within the area of destruction (fig. 36). Microscopically, the osseous lesion shows destruction of the bone by direct contact with the tumor cells and some attempt on the part of the bone to react by fibro-ostosis (fig. 37).

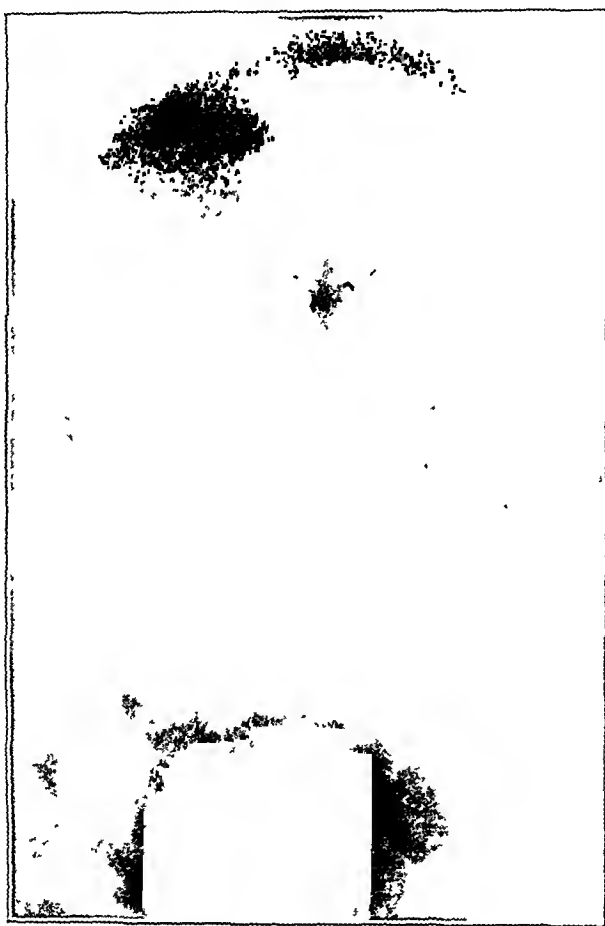


Fig. 36 (path. no. 14500).—Roentgenogram of the skull showing destruction of the bone with slight formation of new bone within the area of tumor invasion.

Hirsch and Ryerson³⁵ reported four cases in which the early diagnosis was that of "endotheliomas" of bone, and they urged complete autopsies in all so-called primary endothelioma of the bone in order to rule out metastases from tumors of the lung.

In one case, pain was relieved by excision of the affected bone.

35. Hirsch, E. F., and Ryerson, E. W.: Metastases of the Bone in Primary Carcinoma of the Lung: Review of So-Called Endotheliomas of Bone, Arch. Surg. 16:1 (Jan., part 1) 1928.

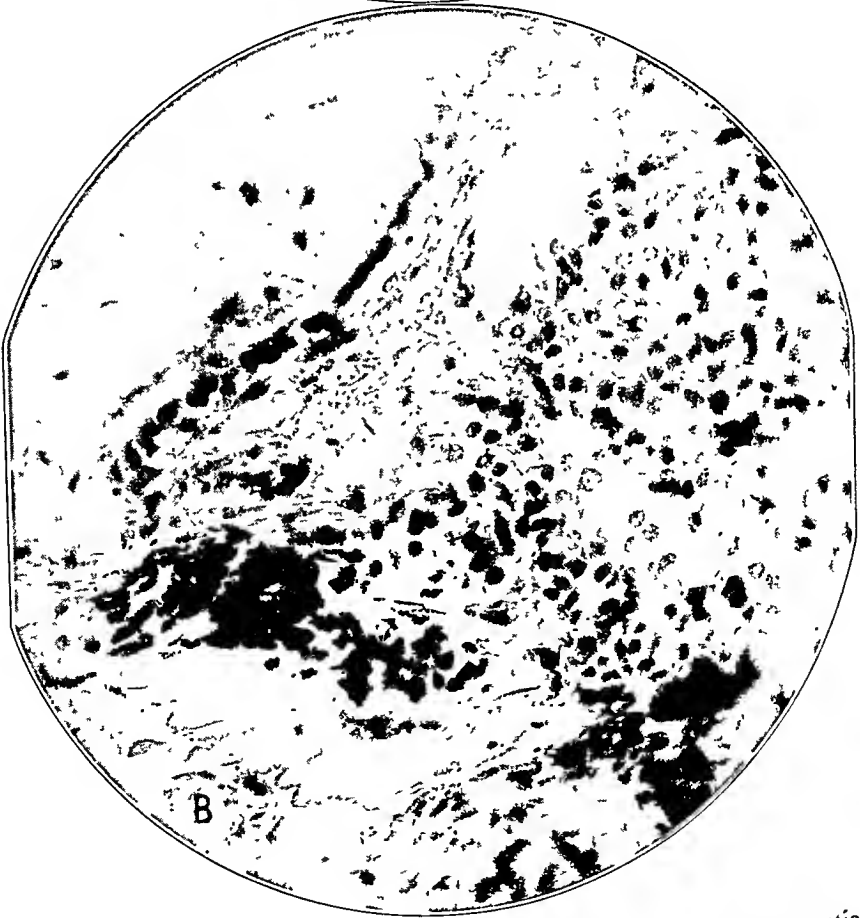
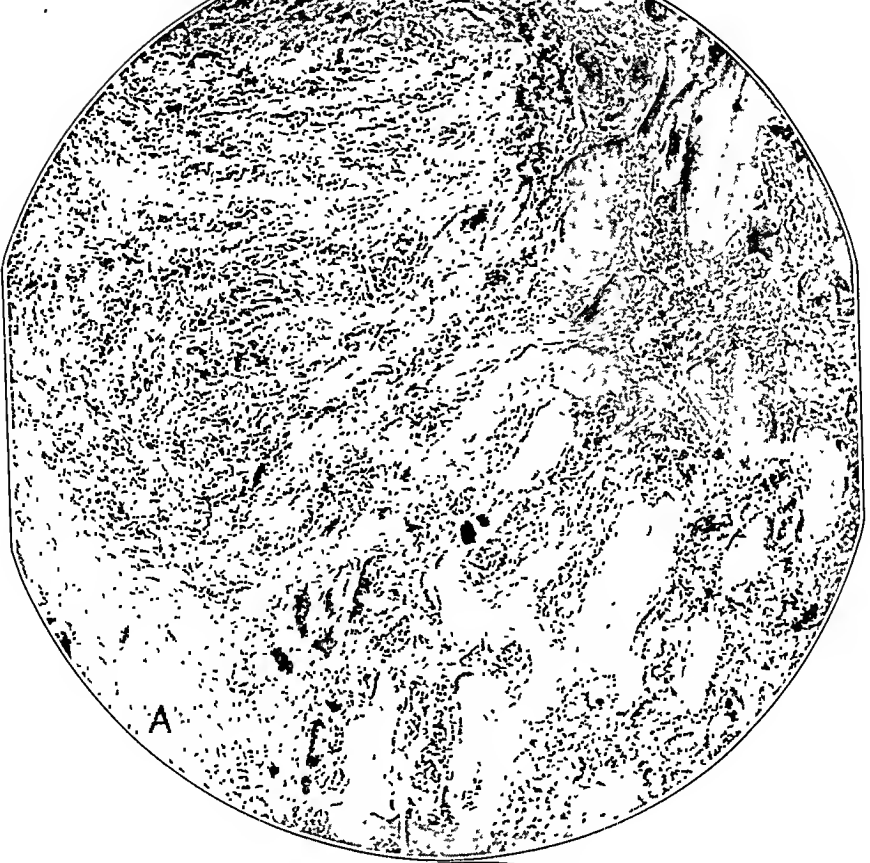


Fig. 37 (path. no. 14500).—*A*, photomicrograph showing the destruction by direct contact with the tumor cells while in areas some attempt is seen on the part of the bone to react by fibro-ostosis. *B*, high magnification of a bone spicule being destroyed by tumor. Note the direct contact between the tumor cells and the osteoid structure.

OTHER PRIMARY TUMORS

Melanomas.—Melanoma developing in a benign pigmented mole is not unusual, but few examples are cited in which metastasis to bone occurs. In 169 cases in this laboratory, only 3, or 1.07 per cent, showed secondary deposits in bone (table 11).

The location in the long bones is about the site of the nutrient vessels (figs. 38 and 39), with marked destruction and expansion of the bone and some invasion of the soft part.



Fig. 38 (path no 32176)—Roentgenogram of a melanoma involving the midshaft region of a humerus. One may observe the marked destruction of the bone with pathologic fracture in this region. At the attachment of the deltoid muscle is seen convex bowing of the bone with subperiosteal formation of new bone on the lateral aspect.

Pathologic fracture occurred in one instance in the middle third of the humerus (fig. 38).

The clinical features of this type of metastasis is one of pain extending over a period of a year or more, occasionally pathologic fracture and ultimately the symptoms of generalized dissemination of cancer. However, there is a patient living seven years and six months following

amputation of the left arm (fig. 38) for a metastatic lesion in the middle third of the humerus (path. no. 32176).

A white man, aged 44, had pain in the middle of the left humerus eight weeks prior to admission. Swelling began soon after and was accentuated by the use of the arm. The examination gave negative results, except for the left arm, where there was a cylindric swelling in the middle third with slight local redness of the skin. The pathologic fracture was found at this examination.

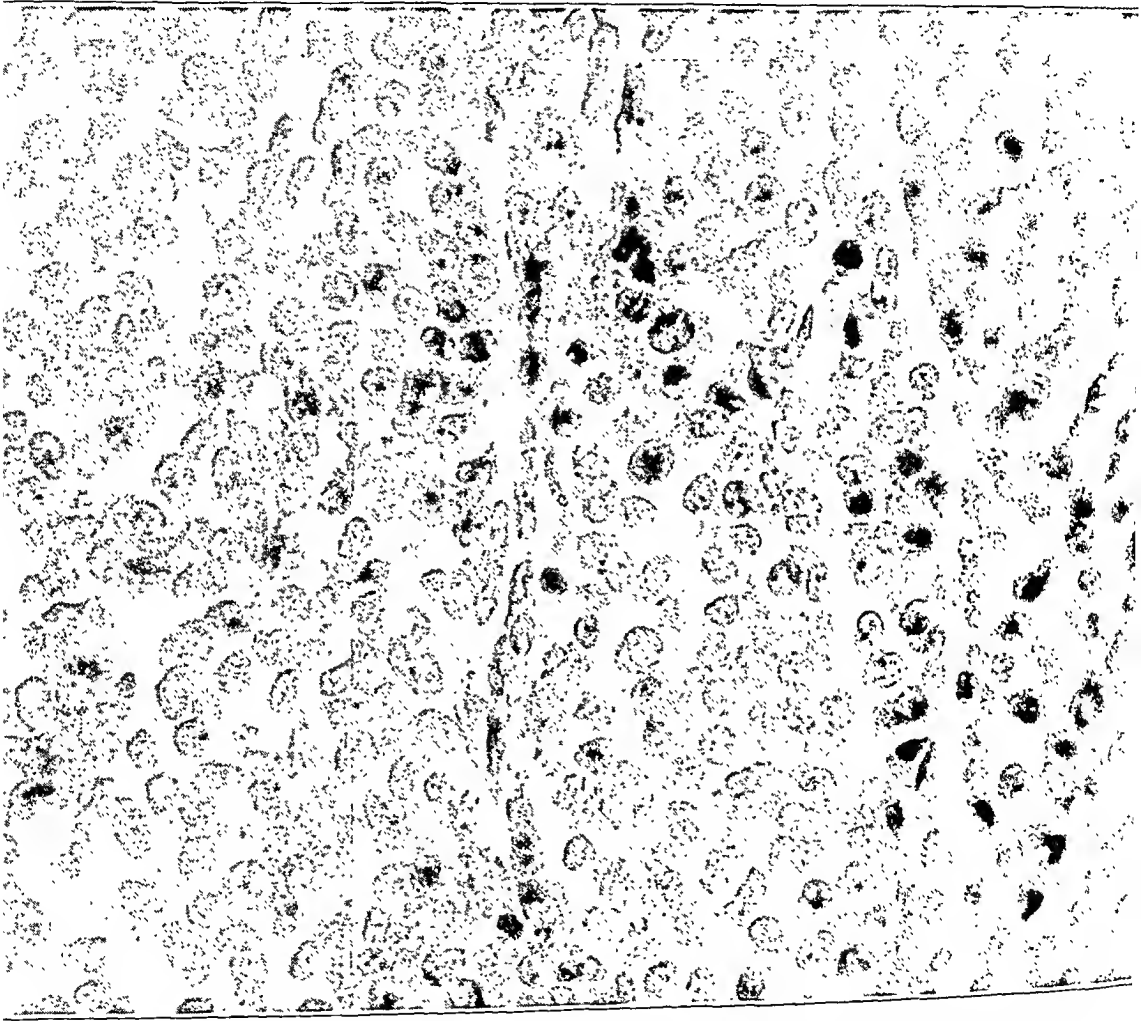


Fig. 39 (path. no. 32176).—Microscopic picture of the tumor depicted in figure 38, showing cells with the morphology of melanoma. Melanin pigment can be seen incorporated in many of the cells.

The arm was amputated, and the microscopic examination (fig. 39) revealed cells with the morphology of melanoma.

Melanotic pigment was found³⁶ incorporated in many of the cells. No

36. Smith, D. T.: Method for Making a Differential Diagnosis Between Xanthomatous and Melanin Tumors from Frozen Sections, *Arch. Surg.* 8:908 (May) 1924.



Fig. 40 (path. no. 40299).—*A* and *B* show an invasion of the skull, pelvis and upper ends of the femurs from an adenoid-cystic, basal cell carcinoma of the nasopharynx. Note the combined destruction and formation of bone within the areas of metastases.

further treatment was instituted, and in January, 1930, the patient was reported well, seven years and six months after the onset of symptoms.

Other isolated examples of metastases from various primary tumors to bone are recorded in the laboratory and are shown in table 11.

An interesting nasopharyngeal tumor of the adenoid-cystic basal cell carcinoma type is to be noted, which after several recurrences and much radium therapy with excision of the primary nasal polyp on many occasions has ultimately metastasized to the skeleton, the patient having lived thirty-six months from the onset of the osseous invasion. The bones involved were the skull, jaw, cervical vertebrae, clavicles, scapulae, all of the ribs, pelvis and femurs (fig. 40).

Dr. John W. Spies of the surgical pathology department of Yale University, in a personal communication, stated that he had collected a large number of these cases. He found that the tumors are usually situated in the region of the nasopharynx or about the buttocks, and that many of them metastasize after repeated recurrences.

METASTASES FROM AN UNDETERMINED MALIGNANT CONDITION

In many instances the clinician is unable to diagnose definitely the lesion of the bone after a thorough examination has been made and roentgenograms of the entire skeleton examined. Even when a biopsy is taken, the morphologic structure of the cells in the microscopic picture are such that little more can be said than that a metastatic lesion is present.

There are thirty-one such cases under analysis in this laboratory, and in none of them is it possible to determine the primary focus. The roentgen criteria in the differential diagnosis of lesions of the bone, as pointed out previously in this paper (see section on breast), plus clinical and laboratory studies, have usually aided in classifying these lesions as metastatic to bone, though in all instances the true nature of the disease is left subjudice (tables 12 and 13).

Little can be gained from detailed analysis of this group. It is to be pointed out, however, that many of these patients were relieved from symptoms of pain for long periods by the administration of roentgen therapy, and in a few instances (path. nos. 39856, 35310, 27929 and 30857), the patients lived from three to eight and a half years following roentgen therapy or amputation of the affected part.

MODE OF METASTASES

Since the time of Virchow and his fundamental work on the knowledge of tumors, many attempts have been made to explain secondary

TABLE 12.—Cases of Undetermined Primary Lesions with Metastases to Bone

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
43226	W	M	45	Carcinoma	Upper third of left femur, left ilium	Left femur	Exploration
42924	..	M	58	Undetermined	1st lumbar vertebra	Laminectomy
42706	W	M	56	Undetermined	Left femur	Left femur below trochanter	Lived 10 mo.
40816	W	F	48	Undetermined	All ribs, dorsal spine, lumbar spine, cervical spine, ilium, scapula, clavicles, humeri, femora	X-rays and lead
40734	..	F	..	Undetermined	Skull, pelvis, thoracic vertebrae, femur, ribs	Ribs, femur	Lived 15 mo.
39914	W	M	60	Undetermined	Right humerus, left humerus spine	Right humerus	X-rays
39856	W	M	21	Undetermined	Skull, upper third of right femur	Upper third of right femur	X-rays	Lived 80 mo.
39506	W	F	66	Undetermined	Ilium, left acetabulum	Ilium	X-rays	Lived 27 mo.
39338	..	M	24	Sarcoma	Right temporal bone
38468	W	M	42	Undetermined	Shaft, humerus and right femur	Lived 48 mo.
37880	W	F	70	Undetermined	Upper third of left femur	Femur
36178	O	F	58	Carcinoma	Middle third of right femur	Femur	Amputation of right leg	Lived 15 mo.
36118	W	M	49	Carcinoma	Shaft of femur	Femur	Curettement	Lived 24 mo.
35838	Undetermined	9th dorsal vertebra, rib, femur
33618	W	F	..	Undetermined	Upper third of left femur, tibia, fibula, left pubic bone	Femur	X-rays	Lived 21 mo.
33310	W	M	..	Undetermined	Humerus	Prophylactic toxin treatment, biopsy and amputation	Living 45 mo.; 1928
35002	W	M	28	Undetermined	Pelvis, 4th lumbar vertebra
34992	W	F	35	Carcinoma	Right clavicle	X-rays	Lived 8 mo.
34300	W	M	67	Colloid carcinoma	Upper third of right humerus	Amputation of right arm
34101	W	M	..	Carcinoma	Clavicle	Resection of tumor
32792	W	F	45	Carcinoma	Frontal bone, scapulae, ischia, fibulae
32446	W	F	..	Carcinoma	Ilium
32229	W	F	40	Undetermined	4th cervical vertebra, 6th dorsal vertebra, ribs, 9th and 12th left, 7th right, femora, left clavicle, ilium	Lived 24 mo.
31018	W	M	55	Undetermined	Left clavicle	Clavicle	Radium, x-rays
30948	..	M	..	Undetermined	Upper third of femur, ilium, and sacro-iliac joint	X-rays
30867	W	F	32	Carcinoma	6th thoracic vertebra	Laminectomy
30857	W	M	52	Undetermined	Ilium, spine	Ilium	X-rays	Lived 36 mo.
30654	W	M	70	Carcinoma	Right clavicle	Clavicle

TABLE 12.—Cases of Undetermined Primary Lesions with Metastases to Bone—Continued

Path. No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
29831	W	F	56	Carcinoma	4th, 5th and 6th cervical vertebrae, skull	X-rays, exploration of skull	Lived 8 yr. 4 mo.
28864	W	M	42	Sarcoma	Midshaft of right femur	Femur	Neoparsphenamine, plaster cast	Lived 4 mo.
27929	W	M	29	Carcinoma	Upper third of right tibia, 6th and 7th dorsal vertebrae	Amputation of right leg	Lived 98 mo.; 10 mo. after amputation
27576	..	M	46	Carcinoma	Rib	Excision of tumor
26264	W	F	54	Carcinoma	Right ilium, right clavicle, cervical vertebra, left parietal bone	Baking, massage, x-rays	Lived 10 mo.
20225	W	M	55	Undetermined	Upper third of right humerus	Antisymphilitic therapy
16245	W	F	49	Carcinoma	Right clavicle, left rib, right tibia, phalanx, right great toe, ilium, sacrum, femur, right rib	Electrical therapy, nonspecific protein therapy	Lived 20 mo.
6830	W	M	50	Carcinoma	Humerus, metatarsal bone	Humerus	Curettement metatarsal bone
1382	W	M	43	Carcinoma	Scapula	Amputation of arm with clavicle and scapula	Lived 7 mo. 2 wk.

TABLE 13.—Involvement of Bone in Thirty-Seven Cases of an Undetermined Primary Malignant Disease

Bone Involved	Number of Cases	Number of Times	Right	Left	Undetermined Side
Pelvis					2
Location (?).....	2	2	..	2	6
Ilium.....	9	9	1	1	..
Ischium.....	1	2	1	1	..
Pubis.....	1	1	..	1	1
Sacro-iliac joint.....	1	1	..	1	..
Acetabulum.....	1	1	..	1	1
Sacrum.....	1	1
Femur					3
Location (?).....	7	8	3	2	1
Upper third.....	5	5	1	3	1
Middle.....	3	3	2
Spine					1
Location (?).....	2	2
Cervical.....	4	4 (twice; number not stated)
Thoracic.....	5	5 (twice; number not stated)
Lumbar.....	3	2 (once; number not stated)	1
Clavicle.....	8	8	5	3	2
Humerus					2
Location (?).....	5	6	2	2	..
Upper.....	2	2	2	..	1
Middle.....	1	1
Lower.....
Rib.....	7	3
Skull.....	6	5	1	1	1
Tibia					2
Location (?).....	2	2	1	1	..
Upper.....	1	1	1	..	2
Scapula.....	3	4	1	1	1
Fibula, location (?).....	2	3	1	1	1
Phalanx.....	1	1	1	..	1
Metatarsal.....	1	1	1

metastatic lesions. Von Recklinghausen³⁷ was among the first to champion the theory of the spread of malignant tumors by the blood stream into the bone marrow, and his deduction was based on the three following points: 1. Metastases in bones occur within the medullary cavity and reach the periosteum only by extension from the interior. 2. When the subperiosteal tissue is invaded, it is always in the region of the large foramina, which serve as a point of egress for the veins. 3. The individual cancer cells in the marrow lie within definite channels, which are arranged in a manner similar to that of the veins present in the marrow.

Proof that the tumor cells lay within the small venous channels was based on the fact that von Recklinghausen could find no blood channels free from the tumor in the invaded areas, and that no known lymphatic channels had been found to exist within the medullary cavity.

Since 1891, there have been many advocates of this theory of the mode of metastases, Paget,³⁸ Piney[†] and Schmidt³⁹ being prominent among the pathologists who favored this view. Piney,[†] in 1922, set forth further evidence in favor of metastases by the blood stream. An anatomic and histogenic analysis was made of the bone marrow, and he found that at birth all of the bones of the skeleton except those of the cranium contained red marrow in which there was no microscopic fatty tissue, and as the person's age increased deposits of fat appeared in the marrow but were not present in equal amounts in all of the bones. In the adult, the vertebrae, sternum, pelvis and most of each rib contained red cellular marrow, the only red marrow in the long bones of the limbs being found in a small area at the upper end of the diaphyses. The small bones of the hands and feet showed complete conversion into fat at a much earlier date. In the bone marrow, he was able to find vascular channels but no evidence of lymphatic vessels. Within the vascular channels, plugs of epithelial cells were found both in the bone marrow and at the sites where the veins emerged through the foramina—points at which carcinomatous metastases reached the surface. These changes were cited by him as evidence in favor of the embolic theory. He set forth the observation of the lack of bone marrow in the small bones of the extremities as a major reason for the paucity of metastases in those regions.

Sampson Handley,¹⁰ in a treatise on cancer of the breast, in 1906, for the first time presented the view that cancer is disseminated by

37. Von Recklinghausen, F.: *Die Fibrose oder deformierende Ostitis die Osteomalacie und die osteoplastische Carcinöse in ihren gegenseitigen Beziehungen*, Festschr. der Assistenten für Virchow, 1891, p. 17.

38. Paget, S.: *The Distribution of the Secondary Growths in Cancer of the Breast*, *Lancet* 1:571 (March) 1889.

39. Schmidt, M. B.: *Die Verbreitungswege der Karzinome*, Jena, Gustav Fischer, 1903.

permeation of the lymphatics, and was of the opinion that the majority of metastases to the bone occurred by direct extension of the tumor cells through the deep fascial lymphatics; that both the humerus and the femur were invaded at points usually in the region where the bone lies nearest the deep fascia or at the point where it comes nearest to the cutaneous surface, and that the bones beneath the knee and elbow were rarely involved, owing to a fatal termination of the case before the invasion of the lymphatics reached these distant locations.

Following this contribution, there have been many advocates of this explanation. Among the more recent investigators, Carnett and Howell¹³ have supported the theory of lymphatic permeation, with one exception: in the case of neoplastic extension within the abdomen they have found the cancer cells permeating the retroperitoneal lymphatics, and in no case have they found the extension of tumor by transcoelomic transplantations as was suggested by Handley. This study is of particular interest in that complete roentgenographic studies were made of a large series of cases of mammary cancer showing metastases in the bone, and they have emphasized the fact that invasion seems to occur first in the region of the primary tumor, with subsequent involvement of other bones in juxtaposition to those already invaded. However, it must be noted that the majority of their cases were in the late stages of the disease, so that either operation was impossible or radical operation was deemed futile.

In the literature cases are recorded with the idea of establishing either the embolic or the lymphatic mode of metastases, and in some instances pathologists, notably Ewing,⁴⁰ have stated that both modes of transmission obtain.

In the analysis of carcinoma of the breast with metastases to the skeletal system in this laboratory, certain facts are presented with a view to verifying the mode of metastases consistent with the data at hand.

Clinically, it was found that the majority of the patients had been treated by radical amputation of the breast early in the disease, and thus many of the lymphatics which might have been a source of tumor invasion were destroyed. This observation is borne out when one comes to study the incidence of bony involvement and finds relatively few of the osseous metastases are in the immediate region of the primary tumor.

When the pelvic bones were involved, there was not infrequently an associated invasion of the heads of the femurs (fig. 15), and the gross and microscopic study in some of these instances showed direct involvement by means of the ligamentum teres, thus establishing further proof that there is an extension of tumor from one bone to another via the lymphatics as well as extension from the primary tumor to the

40. Ewing (footnote 26, pp. 77-96).

regional bones as pointed out by Carnett and Howell. But when one studies the long bones, such as the humerus and the femur, and less frequently the bones of the forearm and those below the knee, especially in the case of single lesions, and notes the absence of invasion in the intervening structures between the primary focus and the distant metastases, one is forced to the conclusion that a vascular route furnished the mode of metastases.

Other groups of primary lesions metastasizing to bone as found in this study have substantiated the facts brought out in the analysis of lesions of the breast and in addition have emphasized in the roentgen and gross study the relation of the nutrient vessels to the metastatic lesions, as well as establishing proof that many bones are invaded by direct extension of the tumor through the lymphatics.

TABLE 14.—*Metastases to the Bone*

Primary Malignant Conditions	Number of Cases	Osseous Metastases		Pathologic Fracture		Patients Living Over Five Years	
		Number of Cases	Per Cent of Cases	Number of Cases	Per Cent of Cases	Number	Per Cent
Mammary carcinoma	1,014	100	5.2	15	15.0	1	1.0
Prostatic carcinoma	1,040	134	12.8	3	0.2	0	0
Carcinoma of the stomach	537	7	1.3	1	14.3	0	0
Colon and rectal carcinoma	497	3	0.006	1	33.3	0	0
Melanoma	169	3	1.77	1	33.3	1	33.3
Uterine carcinoma	86	5	5.6	0	0	0	0
Hypernephroma	63	22	34.9	10	45.4	1	4.5
Ovarian carcinoma	60	1	1.6	0	0	0	0
Testicular sarcoma	42	1	2.4	0	0	0	0
Carcinoma of the lung	24	4	16.6	1	25.0	0	0
Ovarian sarcoma	15	1	6.6	0	0	0	0
Malignant disease of thyroid	15	0	4.0	2	33.3	0	0
Testicular carcinoma	13	1	7.7	0	0	0	0
Undetermined malignant disease	37	...	15	40.5	2	5.4
Nasopharyngeal carcinoma	1	...	0	0	0	0
Squamous cell carcinoma	2	...	0	0	1	50.0
Sarcoma of the soft part	2	...	0	0	0	0
Carcinoma of the bladder	1	...	0	0	0	0
Esophageal carcinoma	1	...	0	0	0	0
Eleve sarcoma	1	...	0	0	0	0
Carcinoma of the liver	1	...	0	0	0	0

With these facts set forth, it would seem that one must accept both an embolic and a lymphatic mode of involvement, and that the particular circumstances of each individual case, such as the duration and the character of primary tumor, together with the method of treatment, will often determine the mode of metastases.

SUMMARY

Three hundred and thirty-four metastatic lesions of bone have been studied with a view to setting forth the important clinical features, x-ray picture, incidence of involvement of the bone, histogenesis, mode of metastases and results of treatment.

One hundred carcinomas of the breast with secondary involvement of the bone were studied. The majority of the primary lesions were

found microscopically to be of the scirrhous type (fifty-eight), with a few instances of adenocarcinoma (six cases), medullary carcinoma (four cases), comedocarcinoma (three cases) and colloid carcinoma (two cases). In one patient, the primary lesion was found to be fibrosarcoma.

The bones most often involved were, in the order of frequency: the spine, pelvis, femur, skull, ribs and humerus, while metastases in the forearm and the lower leg were of infrequent occurrence.

Clinically, pain of a severe rheumatic character was an important feature. When the metastatic foci were located about the spine, girdle pains and many other neurologic manifestations appeared. Occasionally, pain preceded roentgenologic evidence of skeletal metastases from three to eighteen months. The majority of the cases eventually showed a secondary type of anemia with its complications as the disease progressed. In an occasional case reported in the literature it was pointed out that a pseudopernicious type of anemia was present. The terminal phases of the disease were a progressive emaciation, usually with much pain; when the lungs were involved (nineteen cases), respiratory embarrassment with spitting of blood and paroxysms of coughing were added features of discomfort.

Pathologic fracture occurred in fifteen instances, thirteen being in the femur, one in the ilium and multiple fractures of the ribs in the other case.

As shown by the roentgenogram, metastatic lesions of the bone from carcinoma of the breast were found most often to be multiple, presenting themselves as a single focus in only one fourth of the cases. The majority of the solitary foci were in the vertebrae or femur. Two types of metastatic lesions were discussed (osteolytic and osteoplastic). The osteolytic form of metastatic deposit appeared to be the more common one, and in the long bone both types were often found well above the average entrance of the nutrient artery in the case of the femur and above or below it in the case of the humerus. Mottling representing an increase in the density of the bone was often found within the areas of destruction, together with thickening of the cortex above or below the site of metastasis, and it was pointed out that microscopically this proved to be an attempt at osseous repair or fibro-ostosis. The pelvis, vertebrae, skull, ribs, scapulae, clavicles and sternum showed the same typical medullary involvement as those of the femur and humerus. Lack of distortion or bending of the bones was evidenced, due partly to the advanced stage of the disease, partly to roentgen therapy so frequently resorted to and partly also to the age of the patient; fracture was therefore the rule.

The gross and microscopic pathologic changes in the affected bones studied in this laboratory have been described in detail, and abundant evidence was found in favor of a natural tendency of bone to react by fibro-ostosis in an effort to protect itself from further invasion and to rebuild the part already destroyed (fig. 18). It has also been pointed out that following the application of roentgen therapy many of the affected bones revealed a sclerosing or healing reaction.

The differential diagnosis of lesions of the bone from a roentgenographic point of view has been discussed.

Treatment has been emphasized, the patients being divided into three groups: (1) those who first had a radical amputation of the breast; (2) those who had only simple amputation or local excision; and (3) those on whom no operation was performed and who received only various forms of palliative treatment. The therapy as outlined was based on the clinical experience of Dr. J. C. Bloodgood and Dr. Max Kahn. The results obtained from roentgen therapy were relief from pain in many instances and a definite prolongation of life. Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain.

Sixty-three cases of hypernephroma have been reviewed, and in twenty-two instances skeletal metastases were found. The bones usually affected, in the order of their frequency, were: humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum.

The clinical course has been illustrated by a typical case report.

Pathologic fracture occurred in ten patients (45.4 per cent); six times in the femur, three times in the humerus and in one instance multiple fractures of the ribs. In one case, spontaneous pathologic fracture was the first symptom referable to the disease.

The lesions of the bone appeared in the roentgenogram either as single or multiple foci, located in one or more bones. Secondary deposits were found as a single focus in a long bone in the majority of cases (59 per cent). It was pointed out that many of these lesions were at the site of the nutrient vessels, as well as in the heads of the femur and humerus, together with associated metastases of the pelvis in many cases. Little evidence was found in metastases of the bone from hypernephroma of any attempt at fibro-ostosis or formation of new bone within the area of destruction. Early involvement was always represented by a distinct medullary defect, periosteal changes in the roentgenogram being exceptionally rare.

Evidence has been presented to substantiate a hematogenous route of metastatic invasion. Irradiation alone offered as great a chance for the prolongation of life in this group of cases as did surgical intervention alone or surgical measures combined with roentgen or radium therapy.

Metastases of bone as seen in the various cases of primary malignant disease in the male and female genital tract have been presented in detail.

Osseous lesions in carcinoma of the prostate were found most frequently in the pelvic bones, vertebrae and femurs. The patients showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted, with a subsequent progressive emaciation, secondary anemia and excruciating pain in the affected bones. As depicted in the roentgenogram, the metastatic lesions in the bones were predominantly osteoplastic, a characteristic phenomenon in bony deposits from prostatic cancer. On gross examination, these metastatic areas were usually white or grayish nodules, surrounded and interspersed by a marked healing of the bone. This reaction was found to be quite the reverse of that usually seen in other metastatic lesions, and the possibility that the invasive powers of the metastatic tumor were of such moderate character that the bone was allowed to proliferate with sufficient rapidity to keep pace with the invasion of the tumor was set forth as an explanation of this phenomenon. Roentgen therapy offered relief from pain, but was not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection and amputation offered only comfort.

Malignant disease of the testicle with metastases to bone was found to be rare, occurring once in carcinoma of the testicle, and the same incidence was found in sarcoma of the testicle. Case reports were given to illustrate the clinical course. The x-ray picture revealed a destructive type of lesion. In the one case of carcinoma of the testicle with metastases to bone, roentgen therapy seemed to have prolonged life and to have aided the bone in reacting to the tumor growth by recalcification, while the patient with sarcoma of the testicle with osseous deposits received no definite benefit from irradiation and died in a short time following this treatment.

One example of carcinoma of the bladder with metastases to bone has been cited, and its clinical course pointed out.

Five of eighty-six cases of carcinoma of the uterus showed metastases to bone. Two primary tumors were located in the cervix. Clinically varying degrees of pain with disturbance of use in the affected extremities were common symptoms. The clinical course of the advancing disease was dominated by secondary invasion of surrounding organs. The x-ray picture was one of destruction of bone. Treatment proved particularly unsatisfactory in this group of cases.

Two instances of ovarian malignant disease with metastases to bone were found among sixty-nine such cases in this laboratory. Case his-

tories have been presented to illustrate the various clinical features and ultimate clinical course. Roentgen therapy proved of some benefit in one instance.

Involvement of the bone secondary to a malignant condition of the thyroid was found to be of rather frequent occurrence, as presented in the literature.

The clinical course was usually one of progressive emaciation with symptoms referable to the bones that were the seat of metastases. Respiratory symptoms were often prominent when the gland had invaded structures of the neck and mediastinum. The usual microscopic picture of an osteolytic type of metastatic lesion was pointed out. Roentgen therapy proved to be of little avail.

Only 7 in a series of 537 patients who were found to have carcinoma of the stomach presented metastases to the bone. The frequency of involvement of the ribs without metastases to the lungs has been pointed out as an illustration of the lymphatic mode of dissemination. In one instance, a pathologic fracture was found at the lower third of the right femur. A case report has been presented to illustrate the clinical course. An interesting feature of the blood in carcinoma of the stomach with metastases to bone has been pointed out, and a case which showed this type of blood picture has been reported.

Other parts of the gastro-intestinal tract showed an occasional predilection for the skeletal system, which included single examples of malignant conditions of the esophagus, cecum, sigmoid, rectum, ileum and liver.

Carcinoma of the lung with metastases to bone was found in only four patients in a study of twenty-four cases. A wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull. Pathologic fracture was found in the ribs in one case on examination. The clinical course of the disease revealed nothing unusual and was similar to that reported in other metastatic lesions. The x-ray picture showed destruction of the bone with slight formation of new bone, often within the area of destruction. In one case, relief from pain was obtained by excision of the affected bone. Other treatment in this group of cases was not recorded.

Other primary tumors with metastases to bones were melanoma, adenoid cystic basal cell carcinoma of the nasopharynx, epithelioma of the ear and heel and sarcoma of the soft part in the region of the neck.

A group of cases with metastases to bone from some undetermined malignant condition have been presented, and it was pointed out that little could be gained from a detailed analysis of this group, but that in many of these cases roentgen therapy gave relief from pain for long periods.

The modes of metastases have been discussed in detail. The analysis of the cases of carcinoma of the breast with metastases to the skeletal system together with other groups of primary lesions metastasizing to bone was set forth in order to emphasize certain facts with the purpose of verifying the mode of metastases which was consistent with the data at hand. It has been pointed out that both an embolic and a lymphatic mode of involvement were responsible for metastatic lesions of the bone, and that the particular circumstances of each case often determined the mode of invasion.

RETROPERITONEAL TUMORS

REPORT OF CASES *

ISIDORE COHN, M.D.

Professor of Clinical Surgery, Tulane University; Associate
Senior Surgeon, Touro Infirmary

NEW ORLEANS

All cases that present puzzling diagnostic problems are of interest, but this is especially true of cases in which there is known to be an abdominal tumor or in which a tumor is found at operation or autopsy. To the surgeon, the abdominal tumor is of particular interest. He wants to know if it is removable; if so, whether removal will result in permanent cure, and whether by the time the diagnosis is made if secondary growths have formed in other localities which will make cure impossible. It is of interest to know whether the tumors are primary or secondary to a growth at a distance. It is also of interest to know whether they represent local manifestations of general disease.

Because of personal experience, which will form the subject of this paper, I venture to discuss, under one title, some observations that may seem unrelated except for the fact that an abdominal tumor has been present at some stage of the disease.

The group to be discussed will include: (1) retroperitoneal lymphoblastoma (Hodgkin's type) (L. E. L.); (2) lymphosarcoma, apparently originating in the retroperitoneal glands (Miss A.); (3) metastatic tumors of the retroperitoneal lymph glands following teratoma of the testicle (Mr. R.); (4) retroperitoneal sarcoma, secondary to sarcoma of the thigh (Mr. J. L.), and (5) retroperitoneal sarcoma (J. P.).

The first case to be presented should be an incentive to attempt to interpret symptoms better. A review of this case will certainly serve as a shock to any one satisfied with his diagnostic ability, if there is such a person.

The diagnosis was not suspected by any one of the many who saw the patient, and I confess that were I to see another such case I could not now do more than make a guess at the correct diagnosis. I have reviewed the history many times in its entirety and in summary in an effort to find something that might lead to an understanding of the sequence of events so that others might profit by my lack of diagnostic acumen. The end-result is that I am unable to offer many suggestions

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that might clear up the problem, hence I am presenting it for consideration by others.

This case like the others that are reported again proves that the abdomen is a mystery box. The autopsy first revealed the retroperitoneal mass which proved to be a lymphoblastoma. One might well label this case a diagnostic puzzle since so many problems were presented for consideration. When each problem seemed about to be solved, another mystery would appear. The physical signs were at no time in accord with the symptoms. The patient's personal experiences and convictions were factors that affected his emotions to such an extent that it was difficult to evaluate the effects of the disease.

RETROPERITONEAL LYMPHOBLASTOMA (HODGKIN'S TYPE)

CASE 1.—I had an opportunity to observe this patient for six years. My first contact was in 1924, at which time he was complaining of digestive disturbances, severe abdominal pain, particularly in the right iliac region, sour eructations, nausea, vomiting and violent abdominal cramps of short duration. He had had similar attacks for twenty years. Ten years before, such an attack persisted for a week.

A roentgen examination at this time showed a marked pylorospasm and a forty-eight hour stasis in the colon.

An appendectomy was done. A short meso-appendix and an appendix that was curled on itself were found. There was an *anomalous peritoneal fold* which formed a tunnel in which the appendix was hidden from view.

The postoperative convalescence was stormy, particularly because it was necessary to catheterize the patient for several days. Even after his bladder was emptied he had pain which seemed to be out of all proportion to any physical sign. He was fearful of pain.

In November, 1925, he complained of nausea, vomiting and pain which seemed to be relieved by food.

Again in 1926, he complained of nausea before meals. Food would satisfy his discomfort. He also complained of headaches and dizziness. I could find neither physical signs nor roentgen evidence to verify the clinical symptoms which seemed to point to a duodenal ulcer. Efforts were made to treat what I believed to be evidence of an egocentric syndrome. The patient's condition improved under rest, diversion and sedatives.

In December, 1928, he complained of a gnawing pain in the right side of his abdomen two or three hours after eating. He would have pain at night which was sufficient to awaken him, fulness after eating and distention. At times the pain was relieved by eating.

A visualization test of the gallbladder was done, and a report suggesting gallbladder disease was received. There was no evidence of a filling defect anywhere in the gastro-intestinal tract.

On the belief that the emotions might have something to do with his syndrome, the patient was referred to Dr. Lemann for consultation. Dr. Lemann was impressed with the predominance of emotional disturbances and treated him accordingly.

In spite of medical treatment, the symptoms persisted, in fact they became progressively worse. As a last resort it was thought necessary to investigate surgically, and a diseased gallbladder was found. Cholecystectomy was done in

March, 1929; the immediate postoperative course was uneventful. During the patient's convalescence at home, the disease ran a febrile course which was remittent in character. The remissions varied between 99 and 103 F. Urination was frequent and painful. Pus was found in the urine. Marked loss of weight followed an almost complete anorexia.

As it was thought that cystitis and pyelitis were responsible for some of his symptoms, the patient was brought back to Touro Infirmary where Drs. Hume, Pratt and Burns examined the genito-urinary tract. Ureteral obstruction was not found, and cultures from the ureters were repeatedly negative in spite of the fact that pus was found in the urine from the bladder. The urologists suggested that there must be some other source of sepsis than the kidneys.

The leukocyte count varied between 10,250 and 8,500; the neutrophils, between 75 and 85 per cent. Anemia was progressive. Vomiting was persistent. The only way fluid could be supplied was by hyperdermoclysis and intravenous infusions. Chemical examination of the blood presented neither evidence of an acidosis nor alkalosis. At all times the abdomen remained soft.

Fluoroscopic examination showed that the diaphragm was not elevated and both sides seemed to rise and fall normally with respiration. The liver was not palpably enlarged.

From the foregoing evidence we could not believe that a subphrenic abscess, perinephric abscess or an abscess of the liver existed. It did not seem plausible that any other intraperitoneal condition existed such as a subhepatic abscess secondary to the operation or that even an accumulation of the infected bile could be responsible for such a condition. This conclusion seemed to be justified because I believed that some rigidity and probably a palpable mass in the hypochondrium would have been found if either of the latter conditions had existed. There was no jaundice, and the stools were not lacking in color.

Blood cultures were negative. There was a normal or slightly elevated leukocyte count. Septicemia did not seem, therefore, to be a likely diagnosis. The chest remained free from physical signs that would have been present if an empyema or pulmonary condition had been responsible factors. Fluoroscopic examination of the chest by Dr. Henderson showed the pulmonary field to be clear.

On May 2, after all possible causes which could be suggested had been eliminated, including one which was persistently referred to by one of the consultants (multiple abscesses of the kidneys), it was decided, after consultation with Dr. C. Jeff Miller, to do an exploratory operation as a last resort to investigate the conditions about the liver and in the vicinity of the original operative site. Dr. Miller, at the consultation, had suggested that there might possibly be a slight puddling in the vicinity of the cystic duct or near the head of the pancreas.

The incision was made in the upper portion of the previous operative wound. There were no adhesions between the peritoneum and the liver, and a cavity was immediately reached, the lower boundary of which was the stomach, and the upper boundary the liver. The suspensory ligament was free from adhesions.

The liver was large, smooth and red, and evidence of abscesses on the surface was not found. The hand could easily be introduced between the liver and the diaphragm in either direction. Adhesions were not seen between the dome of the diaphragm and the liver. There was only one place in the upper portion of the liver that felt more prominent than the remaining portion, and this was near the midline.

The examining hand was then introduced into the cavity; no fluid accumulation of any kind was found. The stomach was retracted, and we were able to see in the depths that there was nothing suggestive of an abscess. Examination was made by Dr. Miller, who found nothing abnormal. Both of us noted some

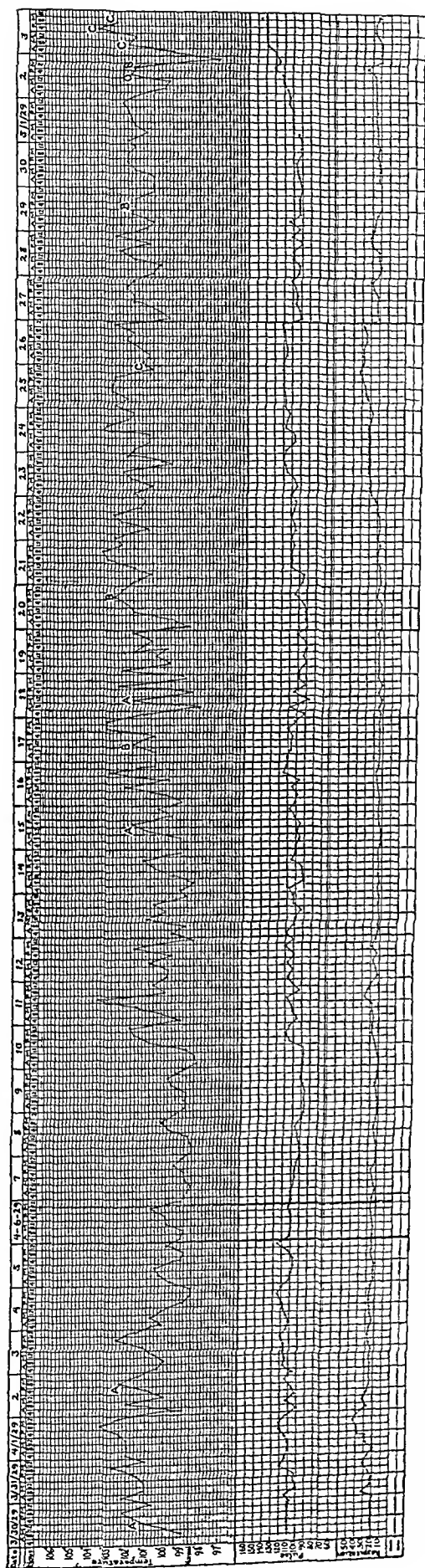


Fig. 1 (case 1).—Graphic chart. *A* indicates the time at which cystoscopy was done; *B*, transfusion of blood; *C*, axillary temperature; *D*, operation.

infiltration near the midline, but since the stomach was well walled off and the gastrohepatic omentum seemed infiltrated and approximated close to the under surface of the liver, no effort was made to break up these adhesions.

The liver was aspirated but pus was not found.

The finger was introduced in the foramen of Winslow, and I could feel nothing pathologic.

The operation did not add any positive diagnostic information. A transfusion was done at the same time.

In spite of repeated transfusions and infusions, which were done prior to the final exploratory operation, the patient grew steadily worse and died several days after operation without sufficient evidence having been found to make any one of the many surgeons, internists and urologists who saw the patient even suspect the real nature of the disease.

The critic who may be inclined to wonder why so much discussion is indulged in before the presentation of the autopsy record can be answered by the outstanding fact that of such men as Matas, C. Jeff Miller, Hume, Lemann, Burns, Pratt and others who saw this case in consultation with me, not one suspected the true status. If this is true, then others may do well to ponder over this history that they may profit, if they can, by this sad experience. Had we known the diagnosis, it is true that nothing would have been of value; in fact, we might have been less hopeful earlier in the case.

The outstanding autopsy observation included large retroperitoneal glands in the vicinity of the stomach, pancreas and duodenum, and an ulcerating lesion of the wall of the stomach. All of the lesions were reported by Dr. Lanford to be "lymphoblastoma of the lymphosarcoma type" (fig. 2).

On reviewing these tissues at a later date at my request, Dr. Lanford reported that they were lymphoblastoma of the Hodgkin's type. Specimens of this tissue were sent to Dr. Bloodgood for examination. Because of Dr. Bloodgood's absence, Dr. L. Clarence Cohn had sections made, and his report is here appended. "Microscopic section showed no germinal centers, no remains of lymphoid architecture, a very cellular tumor, little more stroma than in case 2 (Miss A.), and many large cells of the Dorothy Reed type. I am inclined to think we are dealing with Hodgkin's disease."

Autopsy revealed then a retroperitoneal lymphoblastoma of Hodgkin's disease. There was nothing on which to base such a diagnosis clinically unless one suspects every case of unexplained fever, and that would hardly be justified.

Comment.—When the clinical picture is compared with the implied significance of the original laboratory report a contradiction is noted. The clinical picture was certainly that of an infection, so much so that each one who was consulted in the case sought a source from which the infection could have originated. Closer scrutiny of the laboratory report, if interpreted in the light of recent discussions in the literature, may help. Again, it may add to the confusion as there are certain terms that have been used interchangeably by some authors when discussing diseases of lymphoid structures.

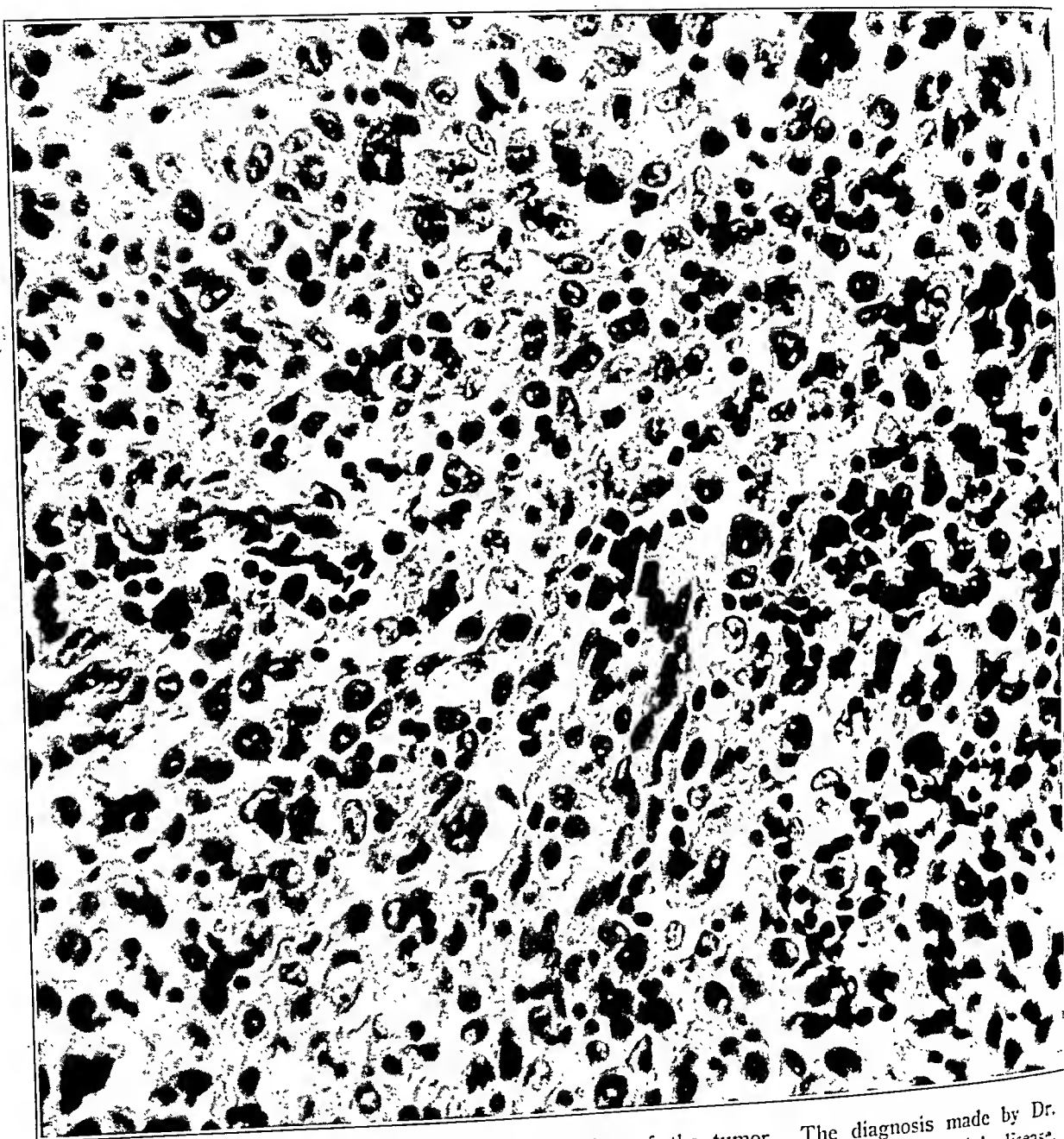


Fig. 2 (Case 1).—Photomicrograph of a section of the tumor. The diagnosis made by Dr. John Lanford was lymphoblastoma of Hodgkin's type; by Dr. L. Clarence Cohn, Hodgkin's disease.

Minot and Isaacs remind one:

Classification leads to clarification and yet confusion arises from sharp distinctions between conditions that have many resemblances; which may be because some of the conditions are but different phases of the same disease. This is the state of affairs for those disorders that may be placed under the same general heading of lymphoblastoma.

It is not the purpose to differentiate here the causative factors that produce retroperitoneal tumors, but simply to direct attention to the presence of such observations. Whether lymphoblastoma, lymphogranulomatosis, Hodgkin's disease or lymphosarcoma are responsible for the glandular involvement is for the moment not my primary consideration, yet one cannot proceed without discussing some of the interesting phases of lymphoblastoma which have been recently discussed in the literature.

From foreign countries, as well as from our own country, there seems to be a general tendency to suggest again that lymphoblastoma or lymphogranuloma is an infection and not a malignant disease in the ordinary accepted significance of the term.

In 1926, Curtis Burnam stated:

The disease presents the earmarks of a chronic infection, the neoplastic nature of the disease has been almost abandoned and is very rarely referred to in the literature.

Again in 1928, Burnam stated:

While it is true lymphosarcoma is a neoplastic, Hodgkin's disease is an infection in all probability.

In acute Hodgkin's disease the general symptoms may completely mask the picture; this is especially true in the abdominal and intestinal type—to such an extent that no gland can be found on clinical examination. It is not uncommon to meet with patients who have had radiotherapy and who present no glandular enlargements and yet show the fever, the weakness, the skin manifestations and other symptoms of the disease. In most instances the active trouble is in the retroperitoneal glands, and the failure to find tumor is due solely to our imperfect methods of investigation.

Fever of an irregular type, both as to daily variations and periodicity, is quite common in Hodgkin's disease and is absent in lymphosarcoma except in the last stages. The high intermittent fever, sometimes reaching a peak of 106 F., and accompanied by chills, and sweats, is particularly distressing. Occasionally in general and frequently in intestinal cases the picture suggests typhoid fever.

In 1929, Ayrosa and Pessoa found a corynebacterium in the cultures from histologically verified cases of Hodgkin's disease, thus adding the weight of their investigations to the theory that Hodgkin's disease is an infection.

Nee and Cailliau, in 1929, stated:

Lymphogranulomatosis is truly an infectious process. The disease has neither the anatomico-clinical appearance nor the histological substratum of cancer; its pseudo-metastases are not destructive like those of cancer and they have all the characteristics of an infectious dissemination.

Does not the quotation from Burnam describe fully the reason for our failure to evaluate correctly the symptoms and arrive at a proximate diagnosis?

While the present case report does not justify a conclusion, such an experience when interpreted in the light of the current literature leads one to an impression that lymphoblastoma, lymphogranuloma or Hodgkin's disease (if those terms are synonymous, and they seem to be accepted as such) is an infection. The fact that this disease is eventually fatal is not necessarily an argument against an infection.

Minot and Isaacs expressed the belief that "one of the big problems of modern medicine is to unravel the nature of the group of conditions that have progressive enlargement of the lymphoid tissue as their most prominent features."

I leave further discussion and elucidation of this subject to those more competent to answer the problems.

The clinical problems are of interest. How long the glandular involvement had been present and what part of the symptoms their presence was responsible for cannot be answered. It is humbling to realize that diagnostic measures during life were not of value, and even the observations made at autopsy are not conclusive.

Such a case as the one reported makes it desirable for one to study with care the clinical manifestations in those cases in which there is known to be retroperitoneal masses with a view to see whether a characteristic syndrome exists. After such a study, I have not been able to find such a syndrome.

RETROPERITONEAL LYMPHOSARCOMA; CHYLOTHORAX

Though case 2 will be reported in detail elsewhere, a summary of it will be included in this presentation because the clinical and pathologic pictures were confused at times with Hodgkin's disease and because the retroperitoneal mass produced obstructive phenomena, ascites, which was at first serous and later chylous, chylothorax and edema of the extremities.

CASE 2.—A woman, 46 years of age, first noticed an enlargement of the glands in her neck one year before she came to the infirmary. During the next twelve months, the axillary, inguinal and epitrochlear glands successively became enlarged. The masses in the glands were discrete and painless. The disease ran an irregular febrile course. There was progressive loss of weight, digestive disturbances,

orthopnea, nausea and vomiting, progressive enlargement of the abdomen and extreme weakness. At the first examination, a diagnosis of Hodgkin's disease was suggested.

The patient was admitted to Touro Infirmary for diagnostic study. The Wassermann reaction of the blood proved to be negative. Other examinations of the blood revealed a secondary anemia, without a leukocytosis and without a marked variation from the normal differential leukocyte count. So far, the results of the examinations seemed to eliminate the diagnoses of lymphatic leukemia, tuberculosis and syphilis. A biopsy was done, and lymphoblastoma not characteristic of Hodgkin's disease was reported.

As the condition progressed, it was necessary to do repeated paracenteses and thoracenteses. The fluid removed from the chest was of a milky consistency, and the analysis of this showed it to contain about 1 per cent of fat. A total of



Fig. 3 (Case 2).—Roentgenogram of the chest. In this case a diagnosis was made of retroperitoneal and mediastinal lymphosarcoma; chylothorax and chylous ascites.

nearly 12,000 cc. of chylous fluid was evacuated from the two pleural cavities during the course of the disease (fig. 3).

At autopsy, enlarged tumors of the lymph gland were found in the mediastinum which in some instances were about the size of an English walnut.

The retroperitoneal lymph nodes were enlarged and matted together and on following up the thoracic duct enlarged structures resembling tumor masses were found at intervals along its entire course which were pressing on it preventing the free flow of fluid.

The broad ligaments of the pelvis were filled with firm, hard nodules, varying in size from that of a small pea to that of a pecan, and which were secondary growths. The tubes presented similar nodules. The uterus was also nodular, presenting secondary growths on its serous surface. The right and left ovaries were infiltrated with secondary growths.

The spleen was about 1 by 10 by 5 inches (2.5 by 25.4 by 12.7 cm.). The cut surface showed that the normal tissues had been largely replaced by new growth, and the appearance of the spleen was somewhat like that of a cross-section of a bologna sausage.

The right kidney contained small secondary growths.

The anatomic diagnosis reported by Dr. Lanford was lymphosarcoma, primarily in the retroperitoneal lymph nodes, with secondary metastasis to the lymph adenomatous structures of the entire body; secondary lymphosarcoma of the kidney, and lymphosarcoma of the spleen.

Blocks of the mediastinal glands and of the spleen were submitted to Dr. Ewing and Dr. Bloodgood.

Dr. Ewing reported on October 6, 1930: "I think that this is a case of lymphosarcoma. Whether it arises on the bases of Hodgkin's disease, as Dr. Stewart thinks, I am unable to state, but I do not find any definite lesions of Hodgkin's disease" (fig. 4).

A specimen was sent to Dr. Joseph Bloodgood. During his absence his associate, Dr. Clarence Cohn reported the following: "Microscopically, the section from the gland showed a lymph gland in which there was no germinal centers. The gland was very cellular and there was a great deal less stroma than we usually see in Hodgkin's disease. It was more like the gland of lymphosarcoma. Nevertheless, there were so many large cells with multiple nuclei suggesting Dorothy Reed cells that I would be more inclined to think of Hodgkin's disease than lymphosarcoma. Section from the spleen showed pretty much the same picture except perhaps there was a little more stroma and not so many of the large multinucleated cells. Nevertheless they were present."

Comment.—The retroperitoneal growths in this case were large enough and so located that they produced obstructive phenomena; in another case, which will be described (case 4), there was a larger mass which did not produce edema or ascites. The mass in this case was located on the left side.

In spite of the large size of the retroperitoneal masses, digestive disturbances were late manifestations in the case of Miss A. (case 2); therefore, the size of the mass is not a determining factor in the production of this symptom. Location near the celiac plexus may be a factor; such is suggested in the first case of this series.

Though the clinical syndrome and the tissues grossly were totally different, there existed confusion in the pathologic changes as well as the clinical diagnosis.

In view of the difficulty which most distinguished pathologists have in arriving at a definite diagnosis, there is some excuse for this case having been considered Hodgkin's disease during life.

RETROPERITONEAL SARCOMA; SARCOMA OF THE THIGH

The next case to be presented is one in which a known retroperitoneal mass existed. This tumor was apparently secondary to a sarcoma on the outer side of the thigh.

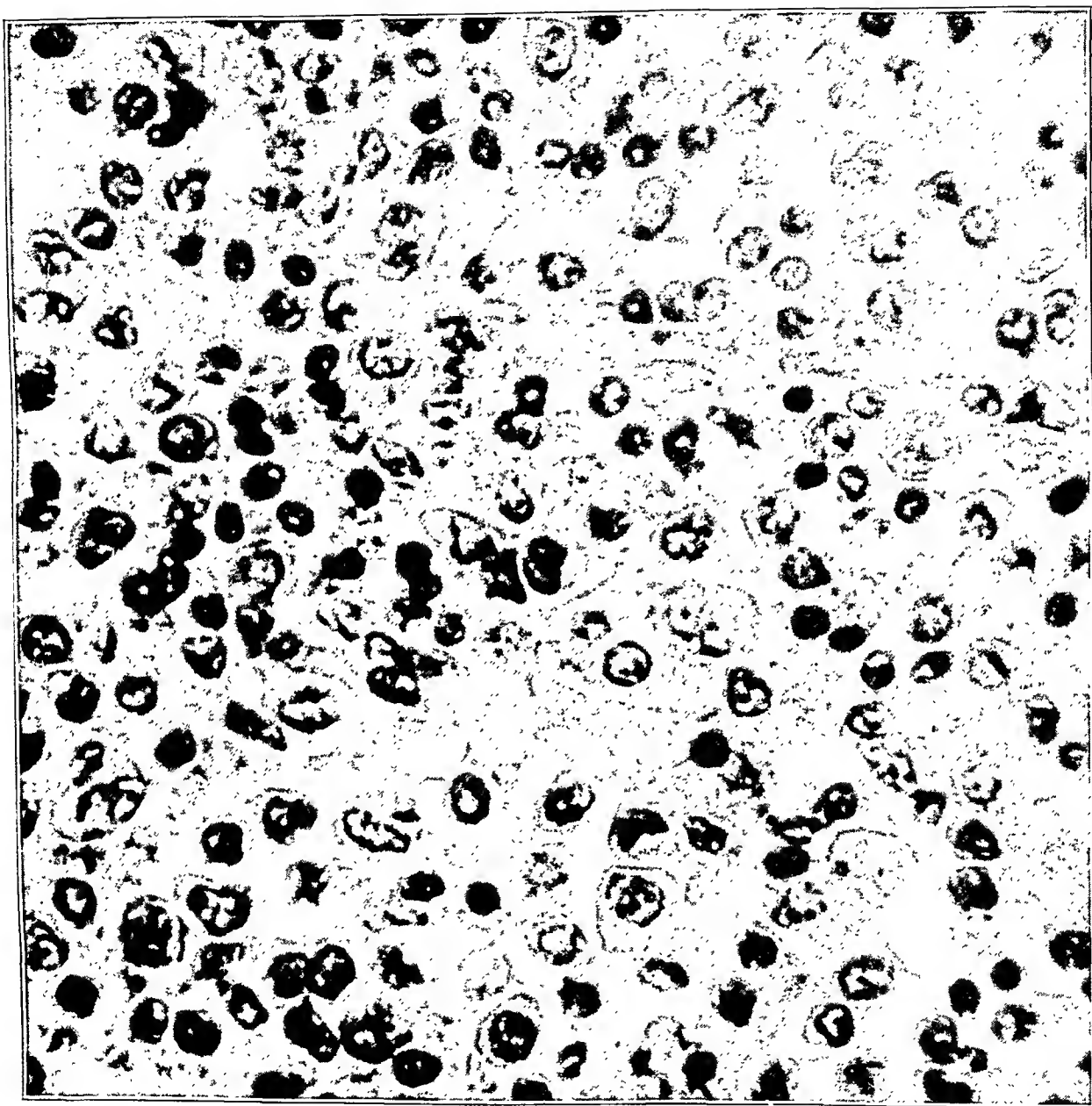


Fig. 4 (case 2).—Photomicrograph of a section of the tumor. The diagnosis made by Dr. John Lanford was lymphosarcoma; by Dr. James Ewing, lymphosarcoma; Dr. L. Clarence Cohn was more inclined to think of Hodgkin's disease than lymphosarcoma.

The following report is taken from a record of the history of Touro Infirmary:

CASE 3.—Mr. J. L., aged 50, was admitted to the infirmary on Jan. 6, 1925, with a diagnosis of lymphosarcoma of the right thigh with retroperitoneal metastasis. The growth on the thigh was excised with the radioknife, and deep roentgen therapy was instituted for the retroperitoneal involvement.

About five months before admission to the infirmary, the patient noticed a mass on the right buttock which rapidly increased in size; at the same time he noticed a swelling in the groin. Other masses had not been found by the patient.

He did not think that he had lost weight; his appetite was fair; there were no digestive discomforts, except that he suffered from constipation.

Physical examination revealed a fairly well developed and well nourished man. The neck was normal. In the right inguinal region there was a mass of glands which was elevated, hard and painful to the touch, and probably deep. Above the brim of the pelvis one got the impression of a retroperitoneal mass. The inguinal glands on the left side were palpable. The liver and spleen were not palpable.

The entire right lower extremity was larger than the left.

Rectal examination revealed a mass on the right side.

On the right thigh there was a mass about 10 by 5 cm., fairly hard, smooth and apparently encapsulated. The overlying skin was soft and freely movable over the mass. There was limitation of motion of the right knee and hip. Flexion of the knee beyond a right angle was painful.

A roentgenogram of the pelvis and chest, on Jan. 7, 1925, did not reveal any evidence of a pathologic process within the chest, except a marked fibrosis throughout both lungs. Metastases to the bone was not found in the pelvis.

The diagnosis of retroperitoneal lymphosarcoma was made for the following reasons:

The question of lymphatic leukemia seemed to be eliminated because of the blood picture which showed a total of 11,500 white cells and of these only 21 per cent were lymphocytes. There was a negative Wassermann reaction, and the question of carcinoma was considered, but there was no primary lesion which we could find that might be considered epithelial in character. A barium sulphate enema did not show any evidence of an obstructive lesion in the rectum or sigmoid colon.

Primary carcinoma of the lymph gland was considered, but on account of its rarity we felt that there was no reason to venture this diagnosis. Hodgkin's disease was considered. The length of time that the disease had remained limited to the inguinal and iliac glands made a diagnosis of Hodgkin's disease unlikely, yet we felt that it was not possible to eliminate it without section of one of the glands. The mass on the thigh and the finding of the glands suggested that we were dealing with lymphosarcoma. Operation confirmed this impression.

In January, 1925, the growth on the thigh was circumscribed and removed with a radioknife. The growth was still encapsulated; it had not invaded the surrounding muscle tissue from which it was readily separated. The growth presented multiple nodulations on its surface, and through the thin capsule it had a gray mottled appearance. The interesting feature of the whole procedure was the lack of burning from the radioknife. (This note was made five and one-half years ago when electrosurgery was a new method in my hands.) After removal of the growth, the wound was sutured with interrupted silkworm suture. On section, the growth presented grossly the appearance of a lymphosarcoma.

According to a laboratory report made by Dr. Lanford, the mass was light gray to light yellow in color, firm in consistency and was composed of large

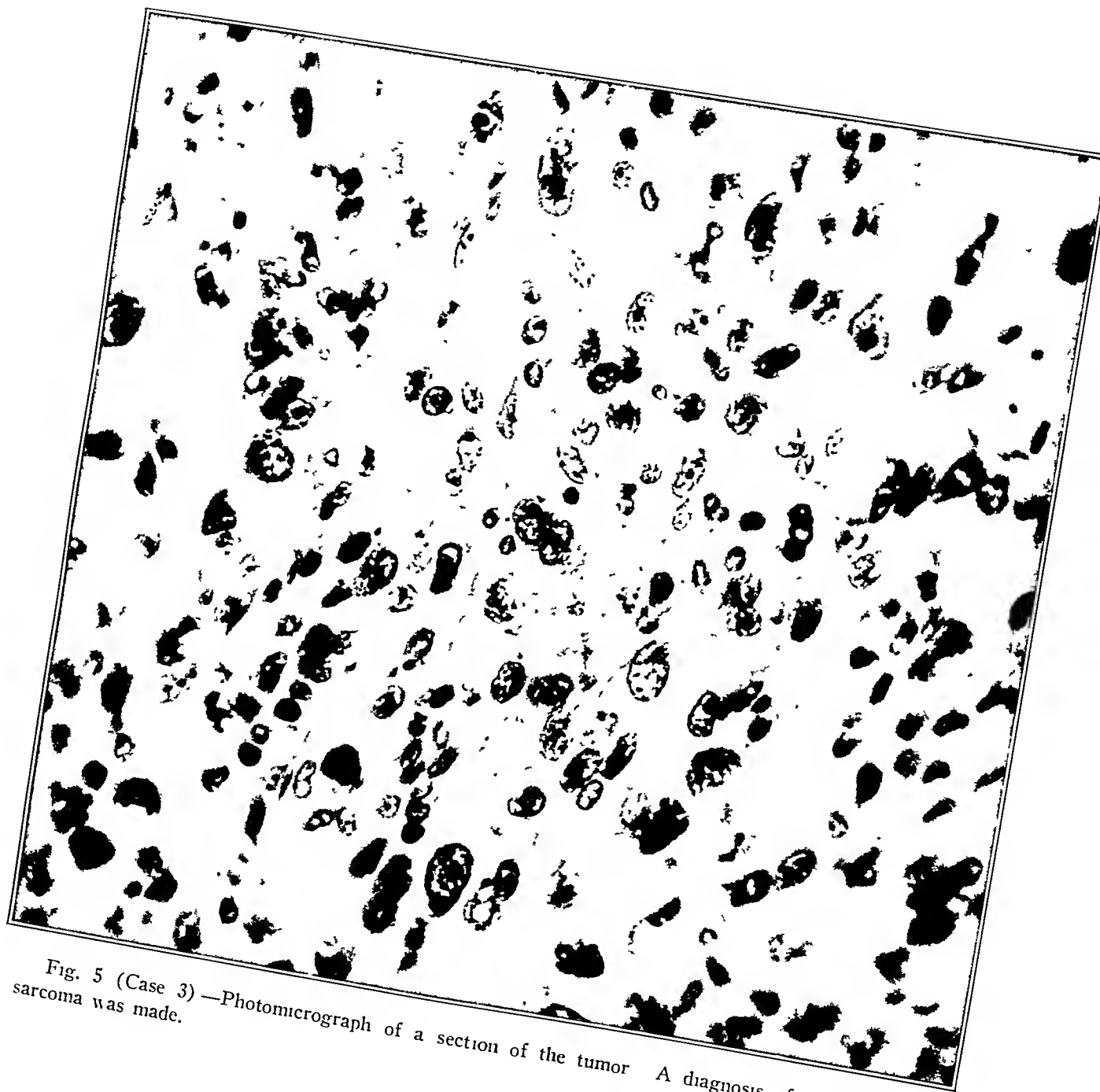


Fig. 5 (Case 3) —Photomicrograph of a section of the tumor. A diagnosis of retroperitoneal sarcoma was made.

nodules measuring about 2 cm. in diameter. Surrounding the connective tissue, there were a large number of blood vessels. A diagnosis of mixed cell sarcoma was made (fig. 5).

The postoperative treatment consisted of deep roentgen therapy and erysipelas and prodigious toxins (Coley's).

On February 23, there was no apparent diminution in the size of the retroperitoneal mass.

The patient was readmitted to the hospital on April 16, 1925, at which time he was scarcely able to walk. Beneath the old scar on the right buttock there was a firm circumscribed mass which was "fixed" to the deep structures, though not adherent nor a part of the bone.

Examination on April 16 showed a firm, painful swelling in the right inguinal region which extended down over the ileum from above the pelvic brim. Masses were felt in the abdomen as before. The right leg was larger than the left. There was no evidence of pulmonary or cardiac pathologic processes.

A report on June 8 showed that for the past month the patient had steadily grown weaker, and his pain had become more severe. His leg became more and more edematous until it was about twice its normal size; the scrotum also was markedly edematous and there was evidence of fluid in the abdomen. He was getting over 24 minims of erysipelas and prodigious toxin (Coley's) with no reaction.

A roentgenogram of the chest taken on June 10 revealed evidence of a large metastasis in the lower lobe of the left lung with a beginning metastasis in the upper right side.

The edema of the extremities and respiratory distress progressively increased, and the patient died on June 16.

On opening the abdomen at autopsy, about 4 liters of fluid were found. The peritoneum was smooth and glistening. In the mesentery a number of large, irregularly lobulated nodules were found. The pelvis was filled with a large, irregular, lobulated mass which had invaded the ileum. The large bowel had been infiltrated by the growth.

The lymph nodes of the hilus of the left lung showed several large masses such as were described in the mesentery. On the pleura, at the posterior axillary line on the left, there were three cystic masses varying from 2 to 10 cm. in width. These infiltrated the ribs. The spleen was small and firm, and the surface was rough. There were small areas of involvement in the liver varying in size.

The anatomic observations were: sarcoma, primary origin unknown, involving the pelvis and the entire gastro-intestinal tract, the liver, the lungs, the pleura, the kidneys and the lumbar vertebrae.

Microscopic examination by Dr. Lanford showed mixed cell sarcoma.

In Dr. Bloodgood's absence, Dr. L. Clarence Cohn, his associate, reported the following: "In this section we found a good deal of stroma, which took a faint stain, and a tumor chiefly of the small round and spindle cell type. It was much different from the tumor of the testicle. The cells did not suggest the cells of a malignant mole. Here and there were multinucleated giant cells. The tumor was not of the lymph gland type. I would be inclined to think the tumor was primary, a sarcoma originating in a bursa, or tumor of a nerve sheath. In a number of cases sarcoma metastasized to the glands."

The outstanding features of this case were: (1) a growth on the outer side of the right thigh; (2) a metastatic retroperitoneal growth; (3) recurrence of the growth on the right thigh; (4) edema of the right leg and scrotum; (5) ascites; (6) late metastasis to the lungs; (7) failure of the roentgenogram to aid in the diagnosis even though an opaque enema was given.

Comment.—All of the evidence of a retroperitoneal tumor presented by this case were late manifestations, and may be attributed to pressure. Such late evidence can hardly be counted on to aid a patient who has a growth sufficiently small to be removed surgically.

RETROPERITONEAL SARCOMA WITHOUT METASTASES

CASE 4.—J. P., a colored man, aged 51, was first seen at Touro Infirmary in the gastro-intestinal clinic on Feb. 2, 1930, at which time he complained of pain in the epigastrium, vomiting, indigestion, belching and constipation. About one month before coming to the clinic he began to suffer with pain in the epigastrium, sometimes extending to the back. After meals he had a feeling of fulness in the stomach which was relieved by belching and vomiting. This vomiting occurred about thirty minutes after meals. The pain in the epigastrium, however, did not seem to have any reference to meals. The patient's appetite was fairly good, but he forced himself to eat because he had lost 22 pounds (10 Kg.) during the last month.

Physical examination showed a well developed, fairly well nourished man, apparently not in any pain and not sick.

The ribs were prominent with sunken interspaces. There was depression and flaring of the lower ribs on the left side. Percussion was hyperresonant. The heart was difficult to outline, but the heart sounds were clear. The breath sounds were distant.

The abdomen was slightly distended, and there was some rigidity on the left side. There was a mass about 4 inches (10.16 cm.) in width and projecting from beneath the ribs on this side. The mass was firm and smooth, dull on percussion and occupied about the same position as an enlarged spleen. The mass was movable on deep inspiration. The liver was not palpable, the upper border of it being at the sixth rib.

The genitals were normal.

On February 2, a test breakfast revealed the quantity to be 50 cc., chymification, good; hydrochloric acid, 22; total acidity, 44.

The patient complained of rather acute pain in the left lumbar region. On aspiration of this region with a 21 gage needle, a small amount of serosanguinous fluid was obtained. The tumor mass was apparently fluctuant.

On February 27, examination showed that the mass was apparently enlarging fast enough to be perceptible from day to day. Enlargement of the spleen was suggested by a superficial mass with a rounded edge, moving with respiration, projecting from under the left ninth rib, and having a smooth surface. There was a projecting mass in the loin with dullness and apparent fluctuation, suggesting the kidney. The genito-urinary department found general enlargement of the prostate. Stasis was not noted in either kidney. The Wassermann reaction was negative. The feces and urine were negative.

Roentgen examination reported by Dr. Henderson (fig. 6) revealed the following: The kidney on the right side was not identifiable, but an opaque catheter was passed up into the pelvis of this kidney. On the left, the ureter passed upward to the upper level of the sacro-iliac synchondrosis, from which point it passed inward to rest anterior to the spine. The pelvis of the kidney was resting anterior to the spinal shadow, and was exhibiting hydronephrosis. Lying to the left side of the kidney was a large retroperitoneal mass which was not springing from the kidney, but was displacing the kidney by pressure. Aside from the hydronephrosis visible, evidence of a pathologic process could not be made out in the

kidney, ureter and bladder, and the type of mass which was displacing this kidney could not be definitely determined. Retroperitoneal sarcoma, however, must be considered as most likely.

On March 3, following a barium sulphate enema (fig. 7), roentgen examination was done. Dr. Henderson made the following report: There was a complete lack of haustral markings in the distal transverse and entire descending colon. This had been converted into a smooth wall tube, and a moderate amount of dilatation had occurred. In addition, there was an alteration in the general distribution of this bowel, the transverse colon resting far down in the pelvis, the splenic flexure resting unusually high up, and there was an alteration of its normal geographic location which was believed to have been occasioned by some rotation.



Fig. 6 (Case 4).—Roentgenogram after pyelography.

In the distal transverse colon about 10 cm. proximal to the splenic flexure an infiltrative lesion could be observed in the wall of the bowel which was partly narrowing and constricting this, but from one side only. The infiltrative type of lesion, the lack of complete encircling of the colon and the alteration in the haustral markings distal to the lesion placed this in the inflammatory class.

On March 11, I noted that the left side of the abdomen and the axillary region presented a number of small pigmented areas. There was a loss of symmetry in the chest. The lower costal margin was elevated sharply at the seventh rib. This caused the costal margin on the left to be above the right side. There was a bulging in the left lumbar region. The left side of the abdomen was distinctly more prominent than the right side which seemed to be retracted and soft; there was some rigidity in the upper segment. Below the umbilicus on the

left side the abdomen was soft; above the umbilicus there was a hard nodular movable mass the edge of which was distinctly palpable about $1\frac{1}{2}$ inches below the costal margin. There was a circumscribed bulging in the left posterior scapular line but no fulness at the costovertebral angle. I suggested a fluoroscopic examination to see if the diaphragm was elevated on the left side, and if the mass moved; also a complete examination of the blood. I believe that the mass was the spleen, but just what the nature of the splenic enlargement was and what the underlying cause remained to be determined.

On March 17, the platelet count showed 275,000 platelets per cubic millimeter (Liles). Examination of the blood showed: total red cells, 3,460,000; hemoglobin, 70 per cent; color index, 1; total white count, 13,500; small lymphocytes, 19; large lymphocytes, 0; neutrophils, 81; eosinophils, 0; basophils, 0.

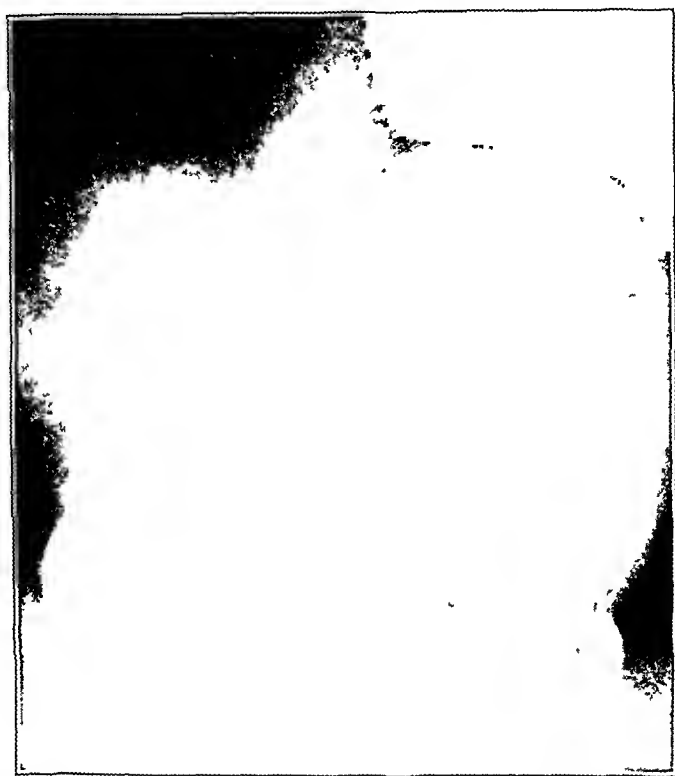


Fig. 7 (Case 4).—Roentgenogram taken after a test meal of barium sulphate. A diagnosis of retroperitoneal sarcoma was made.

Operation was performed on March 10. The preoperative diagnosis was: (1) splenomegaly of unknown origin and (2) retroperitoneal sarcoma; the post-operative diagnosis: inoperable retroperitoneal sarcoma.

An incision was made in the left rectus muscle. Free fluid was not found in the peritoneal cavity. A large lobulated mass was found occupying the entire left side of the abdomen with the bowel overriding and closely attached to the lateral wall. The stomach was adherent to the right side of the mass. The vessels which covered the mass were greatly dilated. The glands in the mesentery were a reddish color and looked like large "dots" on a veil. Exploration revealed a small spleen riding on top of the mass, which was fixed posteriorly to the abdominal wall. It was decided to remove only a small gland. The liver was large, but

there was no evidence of metastasis to the liver. After examination, we felt that any further procedure would result fatally.

Autopsy was performed on August 9. The body was that of a well developed, poorly nourished Negro man measuring about 5 feet, 10 inches (177.8 cm.) and weighing about 115 pounds (52.1 Kg.). The trunk was distorted by a large tumor mass situated on the left side which had pushed up the lower portion of the thoracic cavity and partly obliterated the left peritoneal cavity. There was a healed surgical scar over this area.

The left abdominal cavity was largely obliterated, being entirely occupied by a tumor mass which was covered by the peritoneum and had pushed the intestines to the right and elevated the left thoracic wall. The splenic flexure and descending colon and also the pancreas and the spleen were adherent to the peritoneum over the tumor mass.

The lungs for the most part were crepitant throughout and grayish, and contained many areas of black pigment. The apex of both lungs showed scar tissue, and in the left lung were a number of irregular areas showing caseation, some of which show deposits of lime salts. Evidence of new growth either in the mediastinum or in either lung was not found.

The liver was rather small and firm and slightly nutmeg in appearance.

The gallbladder contained a small amount of bile but was not distorted.

The spleen did not show any evidence of a growth.

The right suprarenal gland was normal and the left was encapsulated in the tissue around the tumor mass and showed no gross evidence of a pathologic process.

The right kidney was covered with fairly adherent perirenal tissue containing some fluid. It was not increased in size and on section showed a normal contrast between the cortex and medulla. The left kidney was encapsulated in the new growth.

The new growth was rather oval in shape measuring about 15 inches (37.54 cm.) in one diameter and 12 inches (30.48 cm.) in the other. It was situated entirely in the retroperitoneal space and was adherent to the peritoneum, the diaphragm and the posterior and lateral abdominal walls and had partly infiltrated into the posterior border of the kidney while over its anterior surface was stretched the suprarenal and pancreas, the splenic flexure of the colon and sigmoid, and the spleen. The tumor was of a brainlike appearance, and the consistency of the whole mass was semifluctuating. On sectioning, it offered no increased resistance to the knife and presented a cut surface that resembled very much that of the brain, being relatively uniform and showing a number of areas of necrosis. Some of the necrotic areas had liquefied.

Anatomic diagnosis made by Dr. Lanford was retroperitoneal sarcoma (fig. 8).

Dr. L. Clarence Cohn, associate of Dr. Joseph Bloodgood, during the latter's absence, reported the following: "Here the stroma predominated; to express it in other words, there was a great deal more of intercellular substance. The cells again were of the large round type. This section did not suggest Hodgkin's disease or lymphosarcoma, but rather a primary retroperitoneal sarcoma not of the lymphosarcoma type, but more like a fascial sarcoma."

The outstanding features of this case were: 1. A large mass was found in the left side of the abdomen which was movable with respiration. 2. Preoperatively the clinical diagnosis of a splenomegaly of undetermined origin seemed likely. 3. Epigastric symptoms caused the patient to come under observation. 4. Roentgen diagnosis proved to be the most accurate preoperative evidence which we had. 5. Emaciation was progressive. 6. At autopsy, there were no metastases to lymph glands or other organs. 7. There were no ascites. 8. Edema of the extremities.

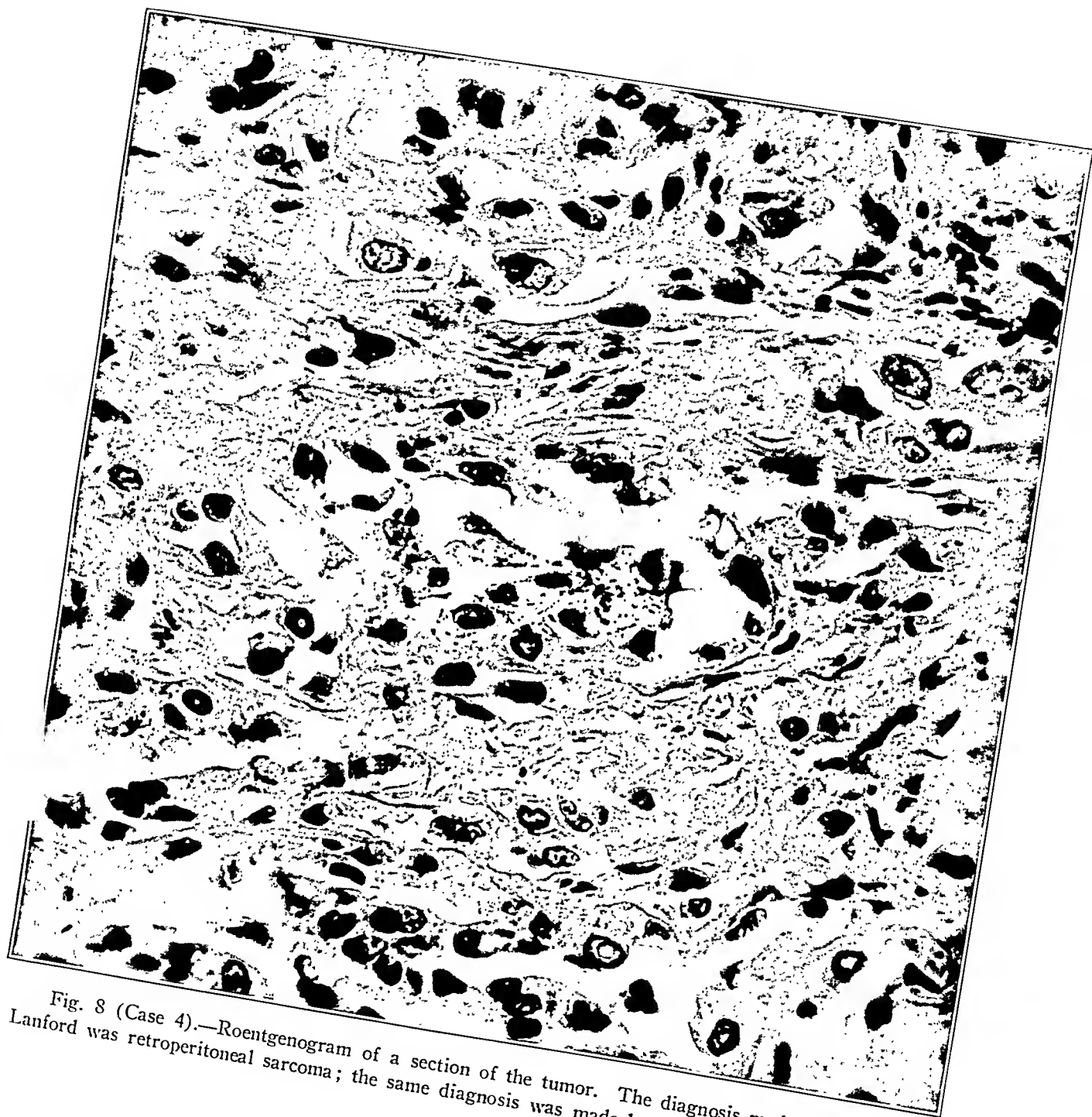


Fig. 8 (Case 4).—Roentgenogram of a section of the tumor. The diagnosis made by Dr. John Lanford was retroperitoneal sarcoma; the same diagnosis was made by Dr. L. Clarence Cohn.

was not present. The lack of edema may easily be explained by the fact that the mass was on the left side and did not interfere in any way with the lymph or venous return.

TERATOMA OF TESTICLE; RETROPERITONEAL METASTASES

In the following case of retroperitoneal metastases from an original teratoma of the testicle, the patient presented as the outstanding disturbance digestive symptoms for which he was referred by the urologist who operated on him originally to Dr. S. K. Simon, a gastro-enterologist. It was through the courtesy of Dr. Simon that I had the opportunity to see this patient.

In order to do justice to many interesting features of the case, an outline of the history will be appended and a discussion of other cases of teratoma in which results were more fortunate will be included.

Three cases of teratoma of the testicle have come under my observations. In one, operation had been done nine months before, and a retroperitoneal metastasis had already developed. I performed the operation in two cases, and the patients are living and apparently well five and two years after operation, respectively.

The case with metastases is of interest, especially in connection with other cases included in this report. The other two are of interest because of the apparently excellent outlook to date. The general topic of teratoma will not be gone into in detail because there are so many excellent reports of large series by Hinman, Coley, Dean, Tanner, Chevasau and others.

In view of the statement of Tanner, that the average mortality based on four years postoperative period was 80 per cent, cases in which the patients survive that period should be recorded.

CASE 5.—Mr. O. R., aged 32, was admitted to Touro Infirmary on Sept. 23, 1925, to the service of Dr. S. K. Simon. The patient's chief complaint was pain in the lower part of the abdomen. In January, 1925, he had been operated on for teratoma of the testicle. In June, 1925, he began to lose weight. During the two months preceding his admission to the hospital, he had lost 25 pounds (11.3 Kg.). His weakness had been progressive, and at the time of his admission was extreme.

About twenty minutes after taking food he would be nauseated and vomit for relief. This progressed to the point that he could hardly retain any food. The abdominal pain was sharp and was located particularly in the left lower quadrant. The patient noticed a mass in his abdomen, for the treatment of which deep roentgen therapy was instituted.

The notes from his record state at the time of his admission that he was fairly well developed but poorly nourished. Examination of the glandular system showed the cervical, epitrochlear and inguinal glands palpable, but not enlarged. Examination of the chest failed to reveal evidence of an intrathoracic pathologic process. The abdomen was flat, symmetrical and muscular. A mass the size of a lemon just to the left of the vertebral column was palpable. The mass seemed to be slightly movable, and it was noted that it apparently had deep attachments.

During the time that the patient was under the observation of Dr. Simon on the gastro-intestinal service from September 23 to October 16, a gastro-intestinal series and other clinical investigations were done to determine if there was any intrinsic gastric lesion. The roentgen report made on November 4 by Dr. Henderson was extremely interesting. The chest showed no evidence of metastatic involvement or other pathologic process. The stomach filled quite well, with no intrinsic filling defects. The peristalsis and motility were considered normal. The stomach itself was quite large and atonic. The pylorus was freely patent, and the food, by manipulation, could be forced through the pylorus along the bulb quite well. The second portion of the duodenum described a wide circle and was markedly dilated and as the food arrived at the lower portion, evidence of obstruction was observed, the meal banking up at this location and being regurgitated into the stomach. An impression was gained of an extrinsic pressure. The six hour observation showed the stomach retaining approximately one-half the meal with no barium sulphate in the small bowel. The twenty-four hour observation showed the meal in the ascending and proximal transverse colon; no filling defect was observed, and the transverse colon was lying well down in the pelvis. The thirty hour observation showed the meal largely having passed from the body, some islands of barium sulphate still remaining in the ascending colon and the proximal transverse colon.

The conclusions made were that there was no pathologic process intrinsic to the gastro-intestinal tube. The stomach was atonic and dilated. The obstruction at the second portion of the duodenum was considered external (fig. 9).

The roentgen observations are of particular significance from a diagnostic standpoint. While one might not be so fortunate as to find such definite evidence of extrinsic causes for obstruction in other obscure cases of abdominal disease, such an investigation should not be overlooked.

During this period the patient also complained of pain after eating, which at times radiated to his scapula. At times he had hiccups. There was no gastric retention.

On October 16, the patient was referred to me for surgical consultation and the following was noted: The abdomen was soft in the lower segments. The inguinal glands were not enlarged. The iliac group could not be palpated through the abdominal wall on either side. Rectal examination did not reveal any mass of retroperitoneal glands. To the left of the vertebral column on a line with the umbilicus, there was a firm mass approximately 4 by 2 cm. which was nodular and freely movable.

Before recommending erysipelas and prodigious toxins (Coley's) or massive radiation therapy, we wanted to see some roentgenograms. Presumptive evidence suggested metastasis, yet the mobility of the mass made one hesitate to make such a diagnosis. In view of the foregoing evidence, I believed an exploratory laparotomy to be indicated.

On October 21, the following operation was done: A high paramedian incision was made on the left side, and the rectus sheath opened; the rectus muscle was retracted outward. When the peritoneum was opened, the stomach was found to be normal and the pylorus patulous; the gallbladder was soft, translucent and emptied easily. The liver was smooth. No adhesions were found.

On the left of the umbilicus and below it lying on the aorta, behind the peritoneum, there was a chain of movable nodular masses; they were of unequal size, the largest being about 1 inch (2.5 cm.) in diameter. These masses moved

with the pulsations of the aorta. The lower limit of the palpable masses was the bifurcation of the aorta. It was evident then that the condition was a metastatic growth in the lumbar lymph nodes, following teratoma of the left testicle. I did not feel justified in attempting to remove them.

On November 2, the administration of Coley's toxins was started. The first reaction was noted November 10. The patient continued under treatment, and the mass apparently diminished in size. He was discharged from the hospital on November 14 to return to the clinic for the administration of the toxins.

On July 19, 1926, he was readmitted to the hospital. In the interim he had lost weight. He was very weak and his general appearance was that of a severe



Fig. 9 (Case 5).—Roentgenogram of the stomach and duodenum after a test meal of barium sulphate. According to Dr. Henderson's report the second portion of the duodenum described a wide circle and was markedly dilated; as the food arrived at the portion, evidence of obstruction was observed, the meal banking up at this location and being regurgitated into the stomach. From this, the impression was gained of an extrinsic pressure. A diagnosis was offered of retro-peritoneal metastasis from teratoma of the testicle.

secondary anemia. On examination, we found a mass the size of a hen's egg located above the clavicle to the left of the sternoclavicular junction. This evidently was a metastasis to Ewald's gland. There was a history of light-colored stools, nausea and vomiting. There was a palpable mass about the size of a hen's egg just above and to the right of the umbilicus. The mass did not give the impression of being attached to the liver, but seemed to be connected with some structure below the liver.

Dulness was found posteriorly over a triangle having its vertex in the midline about the level of the lower angle of the scapula and its base about the level of the costal margins. The breath sounds and fremitus were diminished over this area.

There was a faint diastolic murmur over the third space at the left border of the sternum, and slight enlargement of the heart downward.

At this time another 5,400 mg. hours of radiation was given over the mass in the epigastrium.

Roentgen examination, made by Dr. Henderson, showed that the diaphragm was smoothly contoured; the cardiac and great vessel shadows were not increased: the thoracic cage was bilaterally symmetrical. The pulmonary fields were free from metastasis or other types of lesions. An observation of unusual interest was that a large oval shadow was observed behind the heart overlying the spine; the exact nature of this could not be determined from the roentgenogram of the chest, and it was recommended that this patient return for further study.

It was finally decided that this was a mediastinal growth as fluoroscopy failed to reveal an expansile pulsation in the mass.

The patient was again admitted to the hospital on September 11, at which time radium was applied to the abdomen, 5,400 mg. hours. The supraclavicular glands were still enlarged. The patient was discharged on October 4 and died November 7 at the Charity Hospital. The family refused to grant permission for autopsy.

CASE 6.—Mr. J. B., a white man, aged 28, during April, 1925, noticed an enlargement of the left testicle. There was no history of either an injury or venereal infection. After consulting several surgeons, the patient came under my observation.

On initial examination, I found that the left testicle was about $2\frac{1}{2}$ inches (6.27 cm.) in its long axis. It was hard and freely movable; the epididymis was not enlarged, and the testicle was not adherent to the scrotum. Palpation did not cause pain.

Operation was performed on May 1. An incision was made over the upper portion of the scrotum and the inguinal canal. As soon as the tunica was incised, about $1\frac{1}{2}$ ounces of translucent bloody fluid was evacuated. The tumor was about 2 inches (5 cm.) in length, elliptical and solid; the epididymis was closely adherent to the testis. Nodules could not be palpated in the globus major or minor. The testicle was smooth and had a grayish appearance. The aponeurosis of the external oblique was split, and the vas followed up to the internal ring, ligated high, then dropped back. The spermatic vessels were ligated high. No glands were palpable in the retroperitoneal space. A specimen was given to Dr. Lanford for rush diagnosis and study. He reported at the table a highly cellular growth but was not able to state the exact nature of the tumor.

The laboratory report made by Dr. Lanford follows: The specimen consisted of the testicle, epididymis, vas deferens and surrounding tissue, and tunica vaginalis. The testis measured 6 cm. in length and 4 by 3 cm. It was covered by a smooth and glistening light pink membrane in which ran the blood vessels, which were congested and tortuous. An incision had been made through the testicle and showed a cut surface offering moderate resistance to the knife, light pink in color, homogenous, smooth and glistening. The general appearance was that of a new growth, rather firm in consistency, with edges that were rounded and slightly more hemorrhagic than the center. The epididymis and vas presented nothing abnormal. Another specimen measured 8 by 3 by 0.5 cm., and consisted of the vas deferens and spermatic artery with a large amount of adherent tissue. It presented nothing abnormal. A diagnosis of sarcoma of the testicle was made.

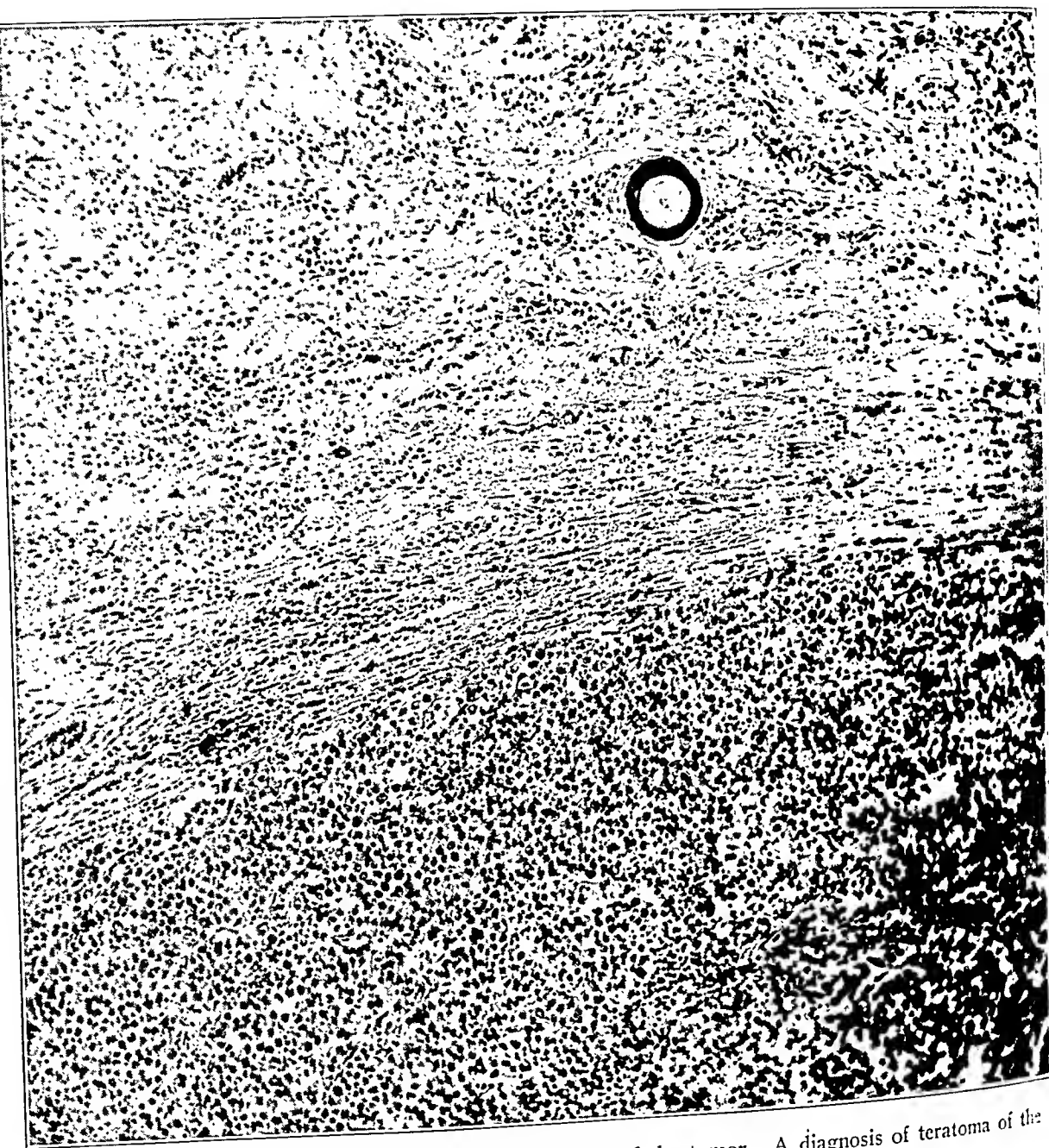


Fig. 10 (Case 6).—Photomicrograph of a section of the tumor. A diagnosis of teratoma of the testicle was made.

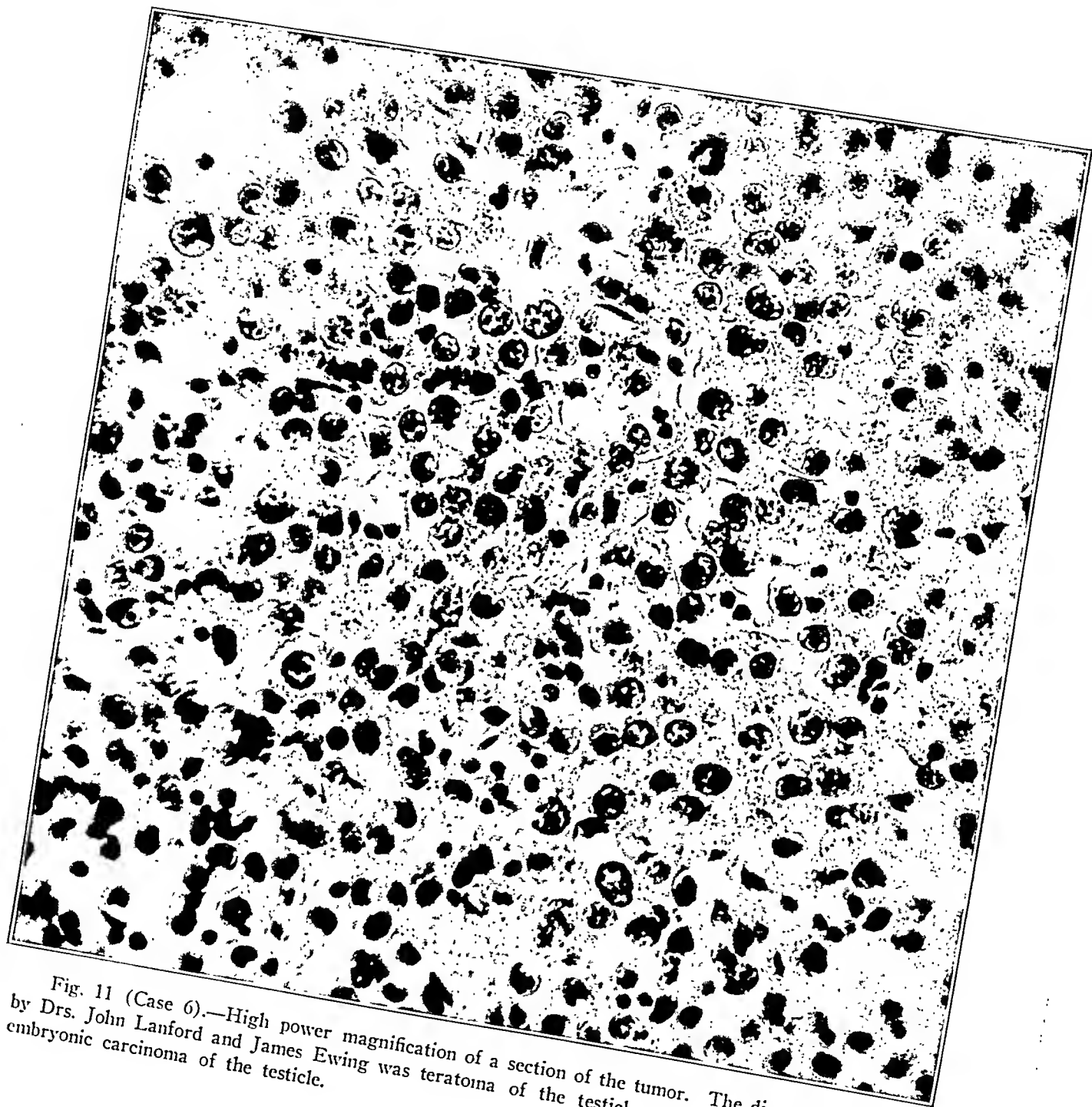


Fig. 11 (Case 6).—High power magnification of a section of the tumor. The diagnosis as made by Drs. John Lanford and James Ewing was teratoma of the testicle; by Dr. L. Clarence Cohn, embryonic carcinoma of the testicle.

A second study of the specimen was made and the following report submitted by Dr. Lanford: The sections from other areas of the testicle showed a slightly different picture from the first examination, and with the use of special stains the predominating cell was found to be epithelial, and, therefore, the condition was most probably made up of several types of structures such as one sees in teratomas of the testicle. The component cells were very embryonal showing many mitotic figures, and while some effort was made to arrange themselves in groups, the stroma was very scanty (figs. 10 and 11).

After the operation, I corresponded with Dr. William B. Coley with reference to any suggestions he would make regarding the after-care. He suggested radium packs and prophylactic treatment with toxins for several months.

On June 8, radium packs were applied over the left iliac region and the left lumbar region, for a total of 5,400 mg. hours. Erysipelas and prodigious toxins (Coley's) were given in increasing doses.

On July 16, the patient's general appearance was excellent. He consulted Dr. Matas in New Orleans and later went to see Dr. Coley in New York. In a personal communication, dated July 9, 1925, Dr. Coley stated that he found him in splendid physical condition.

The specimen was examined by Dr. Ewing for Dr. Coley, and his report coincided with that of Dr. Lanford, that the tumor was a teratoma.

A specimen was sent to Dr. Joseph Bloodgood, and during his absence, Dr. L. Clarence Cohn, his associate, reported the following: "In this case also, I would be more inclined to think we are dealing with an embryonic carcinoma of the testicle rather than a teratoma. In addition to the tumor, we saw normal testicle. The tumor was again of the very cellular large round cell type and there was no evidence of cartilage or myxoma."

At the present time, five years and three months since the operation, the patient is apparently in the best of health and presents no evidence of a recurrence.

CASE 7.—Examination of the abdomen of Mr. A. R. did not reveal any masses, pain, tenderness or rigidity. Examination of the genitals revealed the right testicle to be swollen, tender and hard to the touch. It measured about 10 cm. in diameter; the skin was not adherent or red.

The following operation was done: Incision was made from about the middle of the scrotum upward over the inguinal canal. The aponeurosis of the external oblique was incised; the cord was separated from the surrounding tissues, ligated high, doubly transfixed, and the vas ligated independent of the vessel. Then the testicle was removed with the cord in toto.

The following laboratory report was made by Dr. Lanford: We received an oval mass of tissue which measured about 8.5 by 5 by 4 cm. The mass was fairly firm and nodular being composed of varying sized ovoid masses, loosely connected, ranging in size from that of a sparrow's egg to that of a small hen's egg. The outer surface of the mass was covered by a loose, rather rough appearing, pale pink membrane which slid loosely over the growth. Between the main mass and the irregular mass there appeared an open space which contained a small amount of straw-colored fluid. The irregular mass was found covered with a rather thick, fibrous, glistening white to pale pinkish-yellow coat through which a few tortuous blood vessels could be seen. In the region of the globus minor, there was a small deposit of fatty tissue and a spherical cyst about the size of a pea filled with straw-colored fluid. Section into the mass offered moderate resistance, and there appeared a moist, lobular surface for the most part pale pinkish cream in color and cellular. There were a few scattered, irregularly outlined, yellowish areas of necrosis and near the lower pole there was a rounded



Fig. 12 (Case 7).—Photomicrograph of a section of the tumor. The diagnosis as made by Dr. John Lanford was teratoma of the testicle; by Dr. L. Clarence Cohn, embryonic carcinoma.

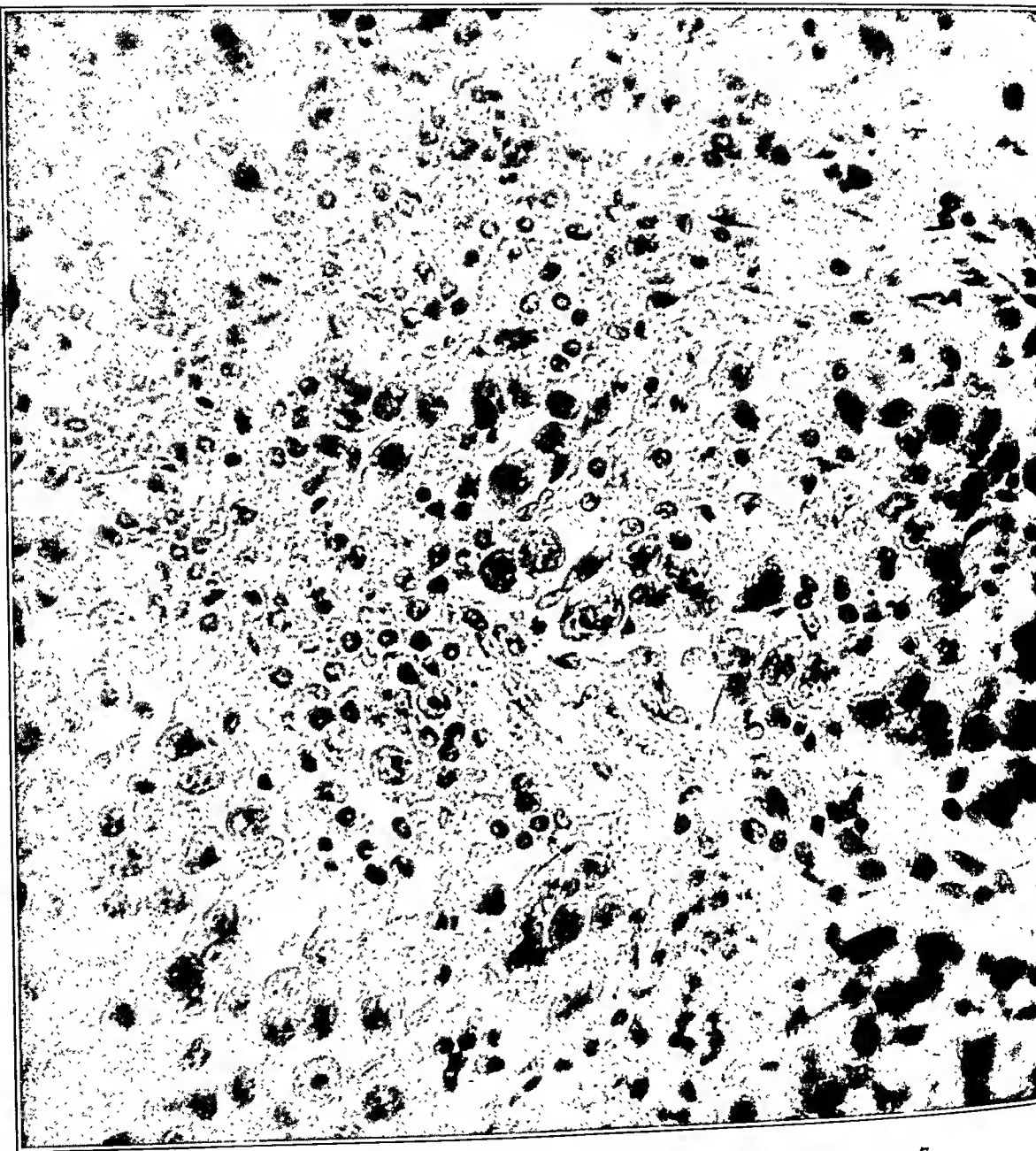


Fig. 13 (Case 7).—High power magnification of the tumor in case 7.

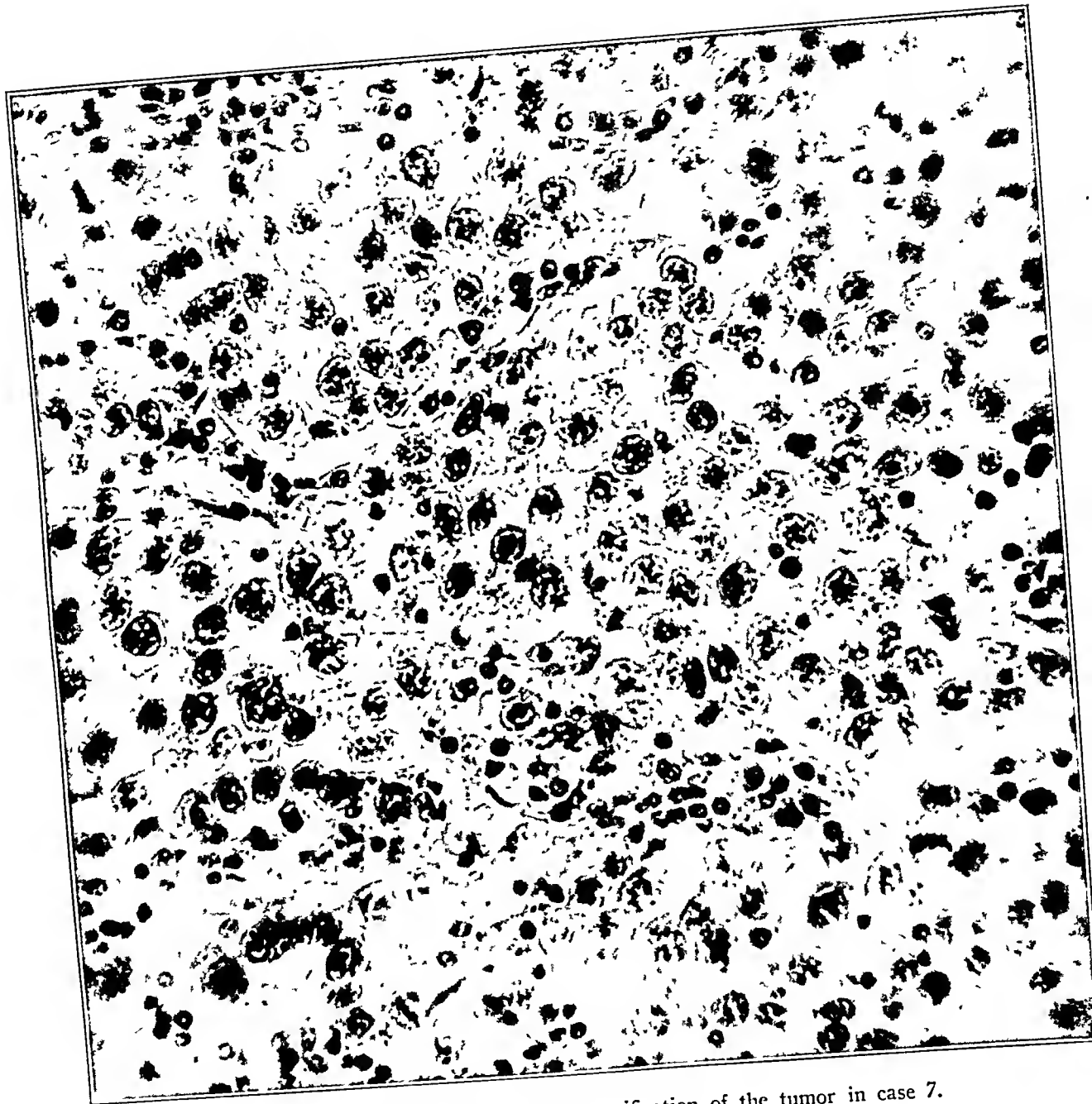


Fig. 14 (Case 7).—High power magnification of the tumor in case 7.

area about 2.5 cm. in diameter, gray to dark red and apparently even more cellular than the other region.

A diagnosis of teratoma was offered by Dr. Lanford. The sections showed many round embryonal cells making but little effort to differentiate, although there were suggestions of glandular structure (teratoma, figs. 12, 13 and 14).

During Dr. Bloodgood's absence, Dr. L. Clarence Cohn, his associate, reported: "Section shows a very cellular tumor in which the cells are arranged chiefly in large clumps and are of the large round cell type. I see no evidence of cartilage or myxoma or anything that would lead us to a diagnosis of teratoma. Therefore, we are placing this tumor under embryonic carcinoma of the testicle."

On June 7, 220 mg. of radium was applied on the right side of the abdomen and the right lumbar region for twenty-four hours.

On June 8, Coley's toxins, 1 minim in 5 minims of freshly distilled water, were given and daily increasing doses were to be given until a reaction was obtained, after which toxins were to be given every other day for three months.

The patient continued to receive toxins. When last seen he had no evidence of a recurrence. The social service reported that in July, 1930, he was working every day and feeling fine.

Comment.—These three cases are too few on which to base any conclusions. They are worthy of comment, however, because the treatment followed certain definite impressions gained through experience and evaluation of the literature.

In the first place, surgeons must not become enthusiastic for a radical operative procedure because of statistical results based on the experience of a few masters who have devoted many years to the perfection of their own technic. I wish to call attention to the enthusiasm of Lane for colectomy and for immediate operation for simple fracture; of Young's enthusiasm for perineal prostatectomy and of Finsterer's enthusiasm for gastrectomy in duodenal ulcers, and last, but not least, of the well known Wertheim operation for carcinoma of the uterus which may well be compared to the radical operation for teratoma as advocated by Chevassu and Hinman in this country.

Most of these procedures have not been accepted and some of them have been entirely discarded, not because of anything inherently wrong, but the magnitude of the procedure did not seem justified for general adoption. Dissatisfaction with routine procedures leads men to try new methods which, though they are associated with greater mortality, seem to result in higher percentages of cures.

The radical operation for teratoma seems logical because its object is to remove along with the involved elements the lymph glands which receive drainage from the diseased areas. I believe that this is essentially the reason that made Hinman advocate radical operation which includes removal of the retroperitoneal glands by the abdominal route in teratoma of the testicle. He has collected seventy cases in which radical operation has been done; ten were personal cases. The primary

operative mortality for the series according to Hinman was 12.6 per cent. Twenty-four patients died of metastases, and six more were known to be living at the time of the report with metastases. According to Hinman, the great majority of those who died of metastases died within one year. He further observed that in cases in which metastases is palpable the condition is inoperable; in addition to this, he says that in twenty-five cases in which radical operation was performed and in which there was no microscopic evidence of metastases in the glands, eight of the patients died later of "postoperative metastases."

One of his conclusions from this last observation should be carefully noted by any surgeon attempting the operation. "Postoperative metastases to the same lymph-bearing area clearly indicates that the original operation rather than being unnecessary, because of failure to find metastases, was insufficiently radical." Analysis of the foregoing statement is essential.

A primary mortality of 12.6 per cent is staggering to say the least; and that is not the mortality rate that the average surgeon would have. I fear that it would be more nearly 25 per cent if this procedure were attempted by the surgeon who removes an appendix or gallbladder with facility. It is also true that an attempt to remove the retroperitoneal glands high up on the aorta is likely to make an otherwise bold surgeon rather timid. Experience in radical operations on the breast where one is working in an easily accessible area proves the incompleteness of the removal of the entire lymph gland-bearing area. Further, if one succeeds in removing all of the apparent gland-bearing tissue, the eight cases cited by Hinman in which the patient died of postoperative metastases, indicate the difficulties incident to recognizing and removing all of the tissue necessary for the operation to be considered radical. Even then one cannot feel safe.

If embryology is to be considered, one should not forget that the abdominal lymph channels find their way above the diaphragm to the mediastinal glands and later by the receptaculum chyli to the lymph glands in the supraclavicular fossae and even into the blood stream. According to Dean, the left supraclavicular glands are involved in 14 per cent of the cases, and the mediastinal in 6 per cent.

By what token can one be sure that these mediastinal glands are not already involved even though there is no roentgen evidence nor palpable enlargement of the supraclavicular glands when operation is undertaken? "Hope springs eternal in the human breast."

Coley expressed the belief that the "number of cures is not sufficiently increased by radical operation or removal of retroperitoneal glands to warrant the very considerable risk of such an operation."

His observation was based on seventy-eight personal cases of malignant diseases of the testicle.

Because high ligation and castration followed by massive doses of radium and erysipelas and prodigious toxins (Coley's) offers some hope for cure without the appalling primary mortality of 12.6 per cent, and probably greater in my hands, I have been led to use the combination, and I must say that I am not sorry.

The patient who presented himself with a retroperitoneal metastases lived nearly two years with a known metastases, during which time, apparently as a result of treatment, he showed marked regressions in the size of the mass. At no time did he present edema or ascites. This is attributable to the location of the metastasis. The extent of the metastases to the mediastinal and supraclavicular glands indicate to my mind that in this case a so-called radical operation would not have prevented the dissemination beyond the diaphragm which would eventually have caused his death. The clinical syndrome that characterized this case included intense abdominal pain, digestive disturbances, emaciation, and the roentgen evidence of extrinsic obstructive phenomena.

The other two cases in which the patients have so far remained well, two and five years, respectively, are of interest because the treatment consisted of orchidectomy with high ligation followed by applications of radium (over the abdomen and lumbar region) and the persistent use of toxins. The plan of treatment needs no defense at my hands. I am taking this opportunity to add my word of confidence in the toxins. Coley's personal results are convincing.

In the beginning of the paper, it seemed to me that it would be necessary to apologize for presenting together a group of cases such as are here included.

Retroperitoneal tumors were discussed before the Southern Surgical Association in 1897 by Dr. Richard Douglas of Nashville. At that time he called attention to the fact that in 1889, Rogowski had collected twenty cases of solid retroperitoneal tumors. Each of these were histologically sarcoma.

Van der Veer, in 1892, discussed the subject of retroperitoneal tumors before the American Surgical Association.

The rarity of retroperitoneal tumor may be more apparent than real. One is aptly reminded by Hertzler, "Whenever one is confronted with a condition the diagnosis of which is exceedingly uncertain and its treatment is fraught with difficulty or disaster, it is more than probable that the number of cases that are reported bears a very uncertain relation to the number of cases that actually are observed." Few men take any great pleasure in reporting a case in which a diagnosis

was wrong and the treatment was a failure. When one has made a blunder and never finds out just what happened, this makes a poor text for a paper.

I found further reason for grouping these cases together for differential diagnostic purposes in some of the frank statements of men like Hertzler. He recorded one case in which a patient 23 years of age presented himself with a tumor extending from the costal margin to the false pelvis. The tumor was irregular in outline, firm and elastic. A diagnosis of hypernephroma had been made by another surgeon following an exploratory incision. Hertzler's own diagnosis was retroperitoneal sarcoma, but operation was not done by him.

At autopsy, he recorded finding a primary nodule in the left testicle, which proved that the tumor was probably a metastasis from teratoma of the testicle. In his case the confusion of metastasis from a teratoma with a hypernephroma is rather comforting, since in one of the cases presented here a retroperitoneal sarcoma was mistaken for a splenomegaly of unknown origin.

My primary object of trying to find diagnostic evidence has led to a review of the observations of previous contributors to this subject with reference to manifestations that were present in other cases.

Douglas stated:

The patients exhibit a pronounced constitutional disturbance. The usual size of the tumor and its location give rise to disturbance of digestion and respiration. The kidneys are frequently displaced and the lymphatics of the digestive tract are partially obstructed consequently the patients are usually emaciated, not infrequently have nausea and vomiting and a pronounced cachexia is developed. The tumors are usually asymmetrical. Contrary to what one would suppose these tumors are sometimes decidedly influenced by respiration.

It was this last manifestation, described by Douglas as long ago as 1897, which influenced me to make the diagnosis of a splenic enlargement rather than a retroperitoneal mass in the case of J. P. The tumor mass in his case extended well below the umbilicus on the left side, was firm, nodular and moved with respiration. This movement with respiration seemed to be confirmed by fluoroscopic examination. No one has yet improved on Douglas' description.

A diagnostic manifestation of considerable importance is the relationship of the bowel to the tumor. Hertzler and others called attention to the fact that the "chief point in determining the retroperitoneal character of any tumor is the determination of its relation to the colon." The colon should be in front or displaced to the side by the tumor. This relationship should be determined by roentgen evidence shown by an opaque meal.

It is generally conceded that retroperitoneal tumors present less mobility than intraperitoneal tumors, though both intraperitoneal and retroperitoneal tumors present roentgen evidence that suggests extrinsic obstruction of the bowel rather than intrinsic manifestations. The more one studies such cases the greater the difficulty in accurate differential diagnosis seems to be.

Just a word in connection with the surgical treatment for these cases. A paragraph taken from Douglas' paper written in 1897 very well summarizes what might be taken to be the present status:

According to Mr. Cripps, they (retroperitoneal sarcoma) do not recur when removed. I think the speaker was very safe in making this assertion, inasmuch as about 95% of the patients die from the operation or before it.

SUMMARY AND CONCLUSIONS

1. This report includes retroperitoneal masses which were apparently primary new growths; some that were metastatic new growths and others corresponded in pathologic signs to the clinical picture which is labeled Hodgkin's disease.

2. Retroperitoneal masses may be present and yet remain undetectable during life by any available diagnostic methods.

3. The roentgen evidence of extrinsic obstructive intestinal phenomena is interesting and diagnostic when present, but the absence of such a sign is by no means acceptable as evidence that a retroperitoneal growth does not exist.

4. Retroperitoneal tumors sometimes move with respiration, thus making it difficult, if the mass is on the left side, to eliminate splenomegalia.

5. The symptoms caused by a retroperitoneal growth are dependent on the location of the growth. Proximity to the celiac plexus causes digestive phenomena, whereas growths even of larger size in other locations may not cause digestive disturbances. Digestive disturbances are not diagnostic as they are present in so many conditions other than retroperitoneal tumors.

6. Anemia is present in many cases of retroperitoneal growths, but is not to be relied on as a diagnostic phenomena.

7. Anemia and digestive disturbances may mislead one to treat the patient for an entirely different condition.

8. Edema of the extremities and ascites are present when the growth is large and when it is so situated as to interfere with the venous return. A growth situated on the right side readily produces edema, whereas a large growth on the left side may not be associated with edema of the lower extremities or ascites.

9. Retroperitoneal masses may be associated with chylous ascites and chylous pleural effusions.

10. Retroperitoneal sarcomas may be primary and productive of metastases. Other retroperitoneal sarcomas may be secondary growths.

11. Some retroperitoneal masses present the clinical picture of an infection, and the autopsy reveals for the first time that the patient had Hodgkin's disease.

12. At present it seems justifiable to conclude that Hodgkin's disease is an infection.

13. When searching for the primary cause of retroperitoneal metastases, teratoma of the testicle must not be overlooked as a possible source.

14. The differential histologic diagnosis is apparently very difficult.

15. So far, my search for a group of manifestations which might help to clear up the puzzling clinical problem produced by retroperitoneal masses has failed to add anything of value.

1522 Aline Street.

LIPOGRANULOMATOSIS (MAKAI) *

M. A. GOLDZIEHER, M.D.

BROOKLYN

Lipogranulomatosis is a rather common disease which is frequently overlooked and misinterpreted. A description of the individual lesions, the whole chain of which constitutes the entity of the disease described by Makai,¹ is repeatedly met with in the literature of the last twenty years. According to Makai, the lesion is due to necrosis of the subcutaneous fat tissue, transformation of its neutral fats into fatty acids or soaps and inflammatory reaction of the surrounding tissue. The result is a granulation tissue, frequently of epithelioid cell character, suggestive of tuberculosis. This similarity is further stressed by the large number of giant cells, some of which are of the ordinary foreign body type, while others are of the characteristic Langhans type. The granulation tissue is finally substituted by fibrous scar tissue in which inclusions of necrotic and even calcified material are met with; or the scar tissue encloses cystlike cavities, the result of liquefaction.

My associates and I observed three cases of lipogranulomatosis at the Crown Heights Hospital on Dr. H. Koster's service. We were also able to demonstrate these cases to Dr. Makai, who happened to be on a visit to this country. A brief description of the three cases follows:

REPORT OF CASES

CASE 1.—Irene D., aged 20, was admitted to the hospital because of several small nodules on the right arm and left thigh. She had noticed their development some years previously, after she had received a number of subcutaneous injections while suffering from pneumonia. There was a hard nodule, the size of a bean, in the region of the deltoid muscle of the right arm. The nodule was slightly raised above the surface, and the skin did not fold over it. There was another nodule about the size of a hazelnut on the external surface of the left thigh. The latter was not as sharply demarcated from the surrounding fat tissue as the nodule on the arm. Neither nodule was tender. On Sept. 23, 1930, the nodules and the overlying skin were removed. Healing occurred per primam intentionem, but was prolonged for fourteen days. After operation, subcutaneous injections of morphine were made into the right thigh, and a painful area of infiltration, the size of a nickel developed, which lasted a week and then disappeared.

Histologic examination of the specimen showed a small round nodule, 5 mm. in diameter, embedded in the fat tissue. It was surrounded by a fibrous capsule composed of dense hyaline fibrils circularly arranged. Inside of this layer, there was a stratum of granulation tissue which was interwoven with heavy strands

* Submitted for publication, Jan. 8, 1931.

* From the Department of Pathology, Crown Heights Hospital.

1. Makai, E.: Klin. Wchnschr. 7:2343, 1928.

of hyaline fibrils. The cells of the granulation tissue were lymphocytes, fibroblasts and larger cells with pale nuclei of the endothelial or macrophage class. The main central part of the nodule was honeycombed. Some of the vacuoles of this area were large and irregular; others were smaller, approximately the size of ordinary or overgrown fat cells. All of the vacuoles were separated by strands of hyaline fibrils and occasional areas of granulation tissue. The latter showed an abundance of large macrophages and cells with foamy cytoplasm suggesting young fat cells. The wall of the cysts and smaller vacuoles was lined by a syncytial seam, with scattered rod or spindle shaped, darkly stained nuclei. Occasionally, these nuclei were grouped eccentrically to present a crescent-shaped

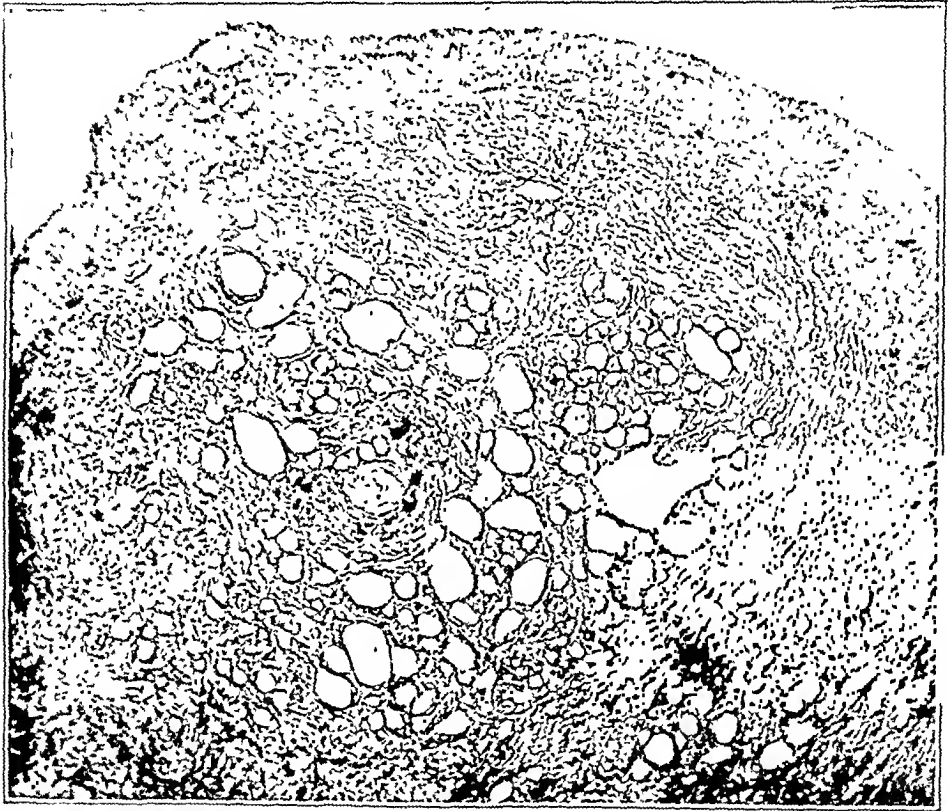


Fig. 1.—Low power view of a nodular lipogranuloma. A fibrous capsule, honeycombed structure and calcification are seen about the necrotic center.

giant cell. Some of the vacuoles contained regular foreign body giant cells, the cytoplasm of which projected irregularly into the lumen. In some of these vacuoles, there was amorphous material which stained a diffuse purplish blue with hematoxylin. The center of the nodule was occupied by another, more densely fibrosed area, the periphery of which showed plentiful amorphous, dark blue-stained deposits. This substance was apparently lime; it surrounded like a ring some poorly staining necrotic tissue. The nuclei in this area were not stained, and only the outlines of the tissue revealed that the area was of a character identical with that of the surrounding honeycombed structures.

CASE 2.—J. B., a man, aged 49, was admitted to the hospital on Sept. 19, 1930, with a history of having been operated on about five years previously for bilateral inguinal hernia. He had noticed the recurrence of a mass shortly after he left

the hospital. At the time of admission, in the right groin there was a large palpable mass which extended into the scrotum. The patient was operated on (Galli operation) and made an uneventful recovery. About a week after his discharge from the hospital, he noticed a small swelling in the upper end of the incision. Wet dressings were applied, and the condition cleared up. One week later, the patient's physician noticed a hard, tender mass under the site of the incision. The patient did not have a rise in temperature, and the mass disappeared after the application of hot wet dressings. This mass recurred and disappeared several times at intervals of four or five days. On November 28, the patient was readmitted to the hospital. At this time the mass was very large, hard



Fig. 2.—Low power view of necrosis of the fat tissue, surrounded by granulation tissue.

and tender, and there were small pinpoint openings along the scar from which clear lymph could be expressed.

The old scar was excised, and dense fibrous tissue was found subcutaneously above the deep fascia. The entire granulomatous mass was excised and the wound closed. The patient made an uneventful recovery. Histologic examination of the specimen showed that the fat tissue was interspersed with areas of hyaline scar tissue. Enclosed therein were numerous foci of groups of lymphocytic cells or small areas of cellular granulation tissue. Single giant cells or small groups of giant cells were also seen, directly surrounded by scar tissue or separated from the latter merely by a wreath of lymphocytes. Several islands of the fat tissue within the scarry area presented a multitude of young, fat cells with foamy cytoplasm in mosaic arrangement. They formed septums between the vacuoles of

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the old fat tissue. In other places, there was evidence of intracellular regeneration of the fat tissue. In the center of this area, where the young fat cells were densest and their cytoplasm stained most intensely owing to the lack of lipid content, there was a small focus of necrosis with needle-shaped rents between the poorly staining necrotic material. Other places of the scar tissue revealed the presence of quite large, oval, single cavities. There was a scanty syncytial seam on the inside of these cysts, with a few scattered pyknotic nuclei. The cysts were enclosed by fibrous connective tissue, and there were no lymph or blood capillaries in their vicinity. They contained a more or less amorphous material, which proved to consist of fatty acids or a mixture of fatty acids with cholesterol esters, as was shown by the results of Benda's or Fischler's stain.

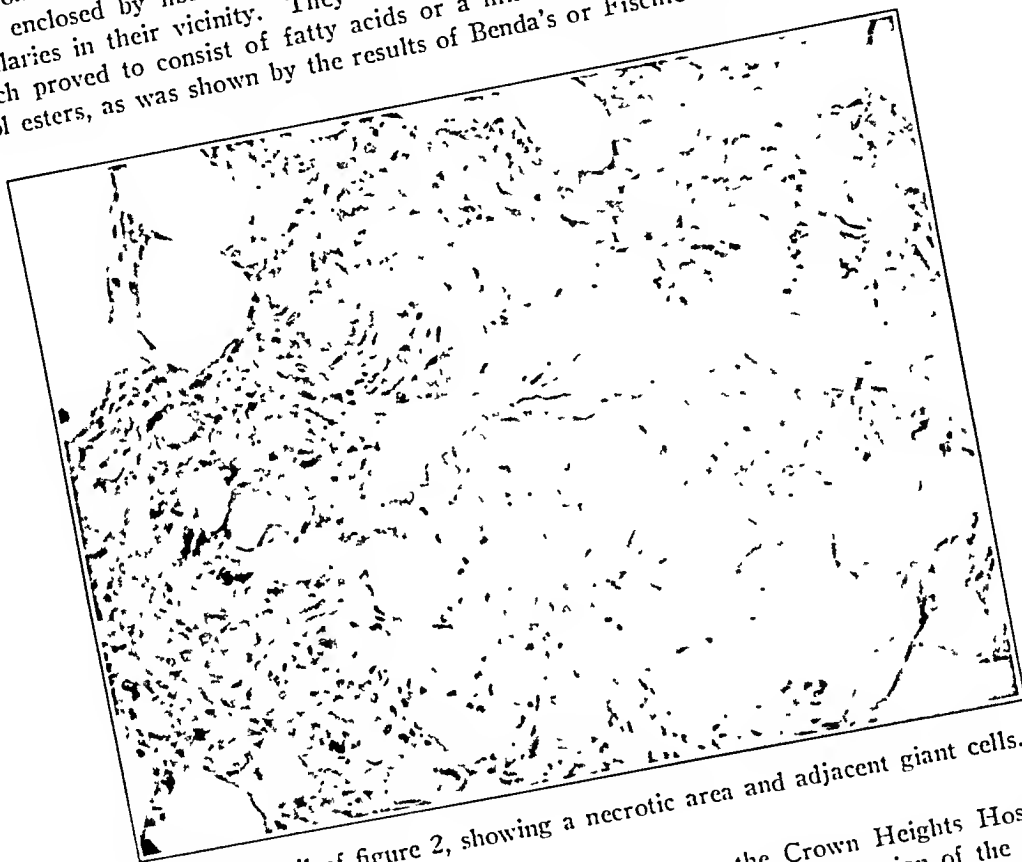


Fig. 3.—Detail of figure 2, showing a necrotic area and adjacent giant cells.

CASE 3.—Rebecca B., aged 37, was admitted to the Crown Heights Hospital with an irregular mass the size of a hen's egg in the medial portion of the right breast. She had noticed the growth of the nodule for the last few months. She could not recall any trauma or any other reason for the growth.

The mass was of an even surface, easily movable and not adherent to the skin. The tumor was excised on Nov. 19, 1930. During the operation, several small cavities opened up which contained a brownish viscous fluid. The diagnosis of galactocoele was made. Healing took place per primam intentionem, but, after two weeks the wound reopened spontaneously, and a hematoma the size of a walnut was found in the fat tissue. An histologic examination was made of the specimen. The glands of the breast showed irregular fibrosis, cystic changes of the glandular parenchyma and cystic dilatation of the lactiferous ducts. The stroma of the glands of the breast and the fat tissue between the lobules of the gland showed an accumulation of round cells, particularly about the blood vessels. There was a small nodule encapsulated by hyaline connective tissue, which consisted mostly

of large epithelioid cells, the projections of which formed a fine reticulum. Between these cells, but particularly surrounding the nodules of epithelioid cells, there was a massive aggregation of lymphocytes. In the center of these nodules there were irregular open spaces which were lined by syncytium, the latter forming giant cell-like structures. In other places, the irregular vacuoles were surrounded by one or several real giant cells from which filament-like projections extended toward the center. On frozen section, crystalline lipid material, probably cholesterol crystals, was demonstrated, surrounded by the pseudopods of the giant cells. In the vicinity of the area described, but directly within the hyaline scar tissue, several giant cells were found each surrounded by a few

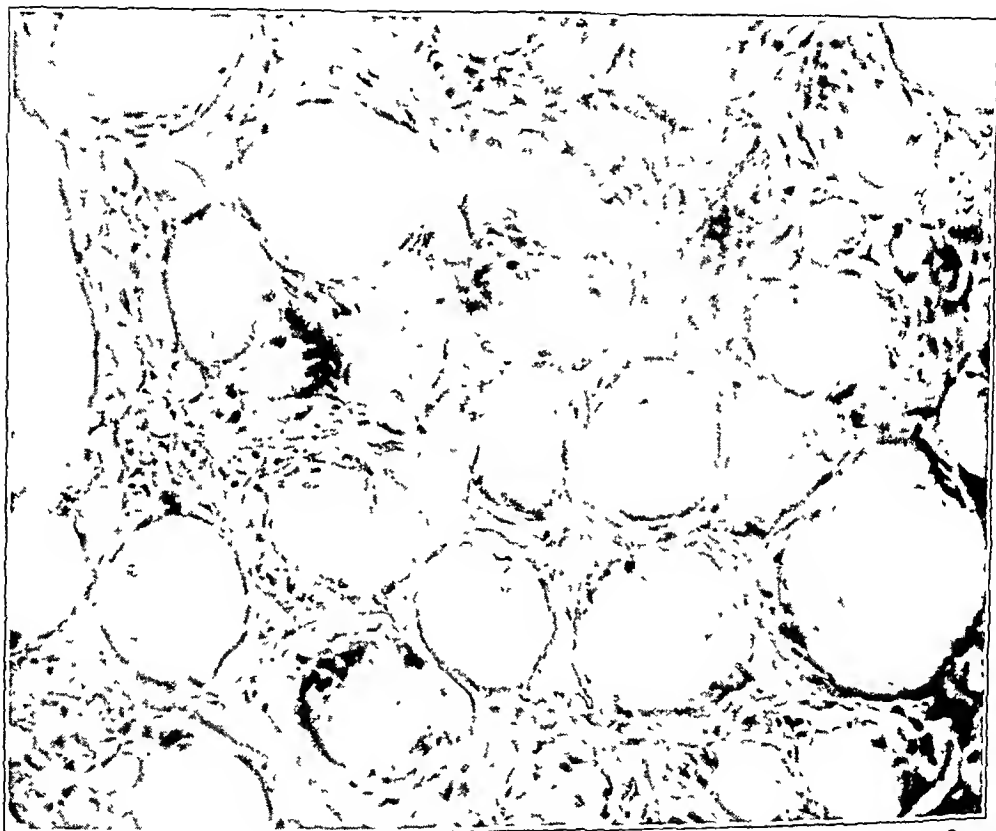


Fig. 4.—Giant cells forming about fatty acid and cholesterol crystals.

lymphocytes. The cytoplasm of these giant cells showed vacuoles divided up by fine protoplasmic filaments and containing fatty material, as shown on frozen section.

COMMENT

In summarizing the observations in these three cases, it can be said:

1. There is a chronic, inflammatory, productive process resulting in the formation of fibrous scar tissue. This tissue develops from granulation tissue which in places is quite cellular and not different from ordinary granulation tissue; in other places, epithelioid cells predominate and form groups resembling tubercles of epithelioid cells. The presence of large giant cells of foreign body type adds to the apparent similarity.

2. Necroses are present, sometimes with the outlines of the decaying tissue fairly well preserved and sometimes transformed into amorphous débris. Diffuse bluish coloration in slides stained with hematoxylin suggests the presence of calcium soaps, as seen in pancreatic fat necrosis. Needle-shaped rents indicate the former presence of cholesterol crystals which can actually be demonstrated in frozen sections. Massive deposits of lime in and about the necrotic foci were present in two of the cases.



Fig. 5.—Large, single giant cell surrounded by granulation tissue.

3. The changes in the fat tissue can be divided into two groups. On the one hand, there is a new formation of small fat cells. Their lipid content does not dissolve in the paraffin sections. Their cytoplasm is finely granular and moderately basophilic. These young fat cells seem to form between the old fat cells, but their endogenous development within the body of the old cell is actually demonstrable in many instances. The remaining fat droplet then appears, surrounded by cells which are sometimes multinuclear. The other type of change consists in the appearance of large vacuoles, from two to three times as large as an ordinary fat cell, but sometimes exceeding these dimensions many times. Some of these fat cysts are large enough to become visible to

the naked eye. These cysts are lined with a syncytial protoplasmic seam in which scattered nuclei may be seen, or the nuclei group together eccentrically and appear in the form of a crescent-shaped giant cell. Fat cysts occur singly or in groups which are separated by hyalinized connective tissue fibrils. They usually contain fatty material, particularly fatty acids, more or less diluted with serous fluid.

The changes observed in these three cases do not cover the whole scale that previous observers have attributed to the cycle of lipogranuloma. Abrikossoff² classified the changes in five groups. The first

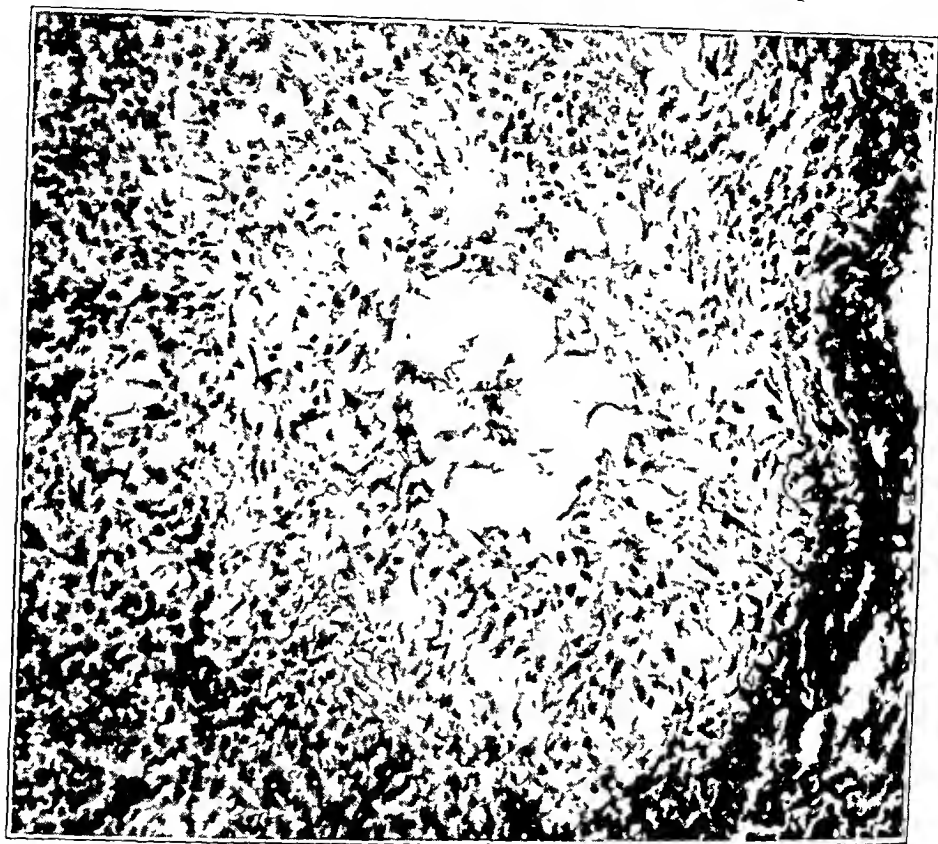


Fig. 6.—Epithelioid cell nodule with central vacuole.

includes the early forms of epithelioid cell granulations with subsequent progressive fibrosis. The second is represented by the appearance of cysts, some of which may fill up with serous fluid after absorption of their fatty content. The third appears as a completely fibrotic nodule characterized by many small foci built by concentric arrangement of their hyaline fibrils. The fourth stage is closely related to the previous one and differs in the presence of calcareous deposits in the center of the concentric hyaline structures. The fifth group presents the picture of complete petrification and corresponds to that which is known as a fat tissue stone.

2. Abrikossoff, A.: *Verhandl. d. deutsch. path. Gesellsch.* 24:57, 1929.

The various authors mostly agree as to the histogenesis of lipogranuloma. The consensus is that the changes set in with necrosis of the fat tissue followed by the formation of granulation tissue, progressive scarring and finally calcification. The formation of giant cells and of cysts, particularly the larger ones with serous content, however, has given rise to diverging interpretation. Makai expressed the belief that the giant cells are at least partly the products of proliferating capillary endothelium, and observation of serous cysts has led several Russian authors (Schujeninoff³ and Kedrovsky³) to classify these lesions as

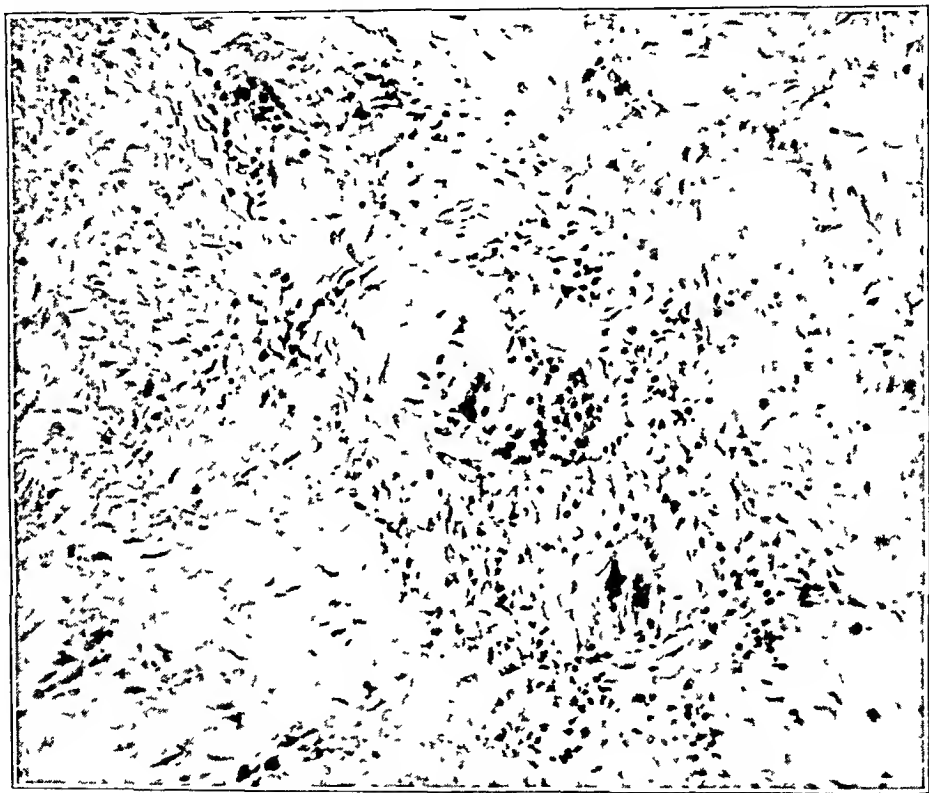


Fig. 7.—Giant cells in the scar tissue.

“cystic lymphangitis.” Abrikossoff pointed out that there is no need for this assumption. The formation of giant cells of this type is closely linked with two processes: the regeneration of fat cells and the response of macrophages to the presence of free extracellular fatty material. Special stains (Sudan, Benda’s and Fischler’s stain) reveal the presence of fatty material in the cytoplasm of the giant cells and identify them as genuine “foreign body” giant cells in contradistinction to giant cells such as occasionally form through hasty and incomplete division of proliferating endothelium. Abrikossoff drew attention to the simi-

3. Quoted by Abrikossoff (footnote 2).

larly erroneous interpretation of changes commonly observed in dermoid cysts, in cases in which their walls had been invaded by some of the fatty material. The giant cells that develop in such places have been derived from the endothelium of lymph vessels (Stuebler,⁴ Schottlaender⁵ and Gentili⁶), but it seems more logical to ascribe their origin to proliferation of ordinary macrophages.

Etiologic factors in the pathogenesis of lipogranulomatosis are manifold. Whether the cause is trauma, inflammation or a circulatory dis-

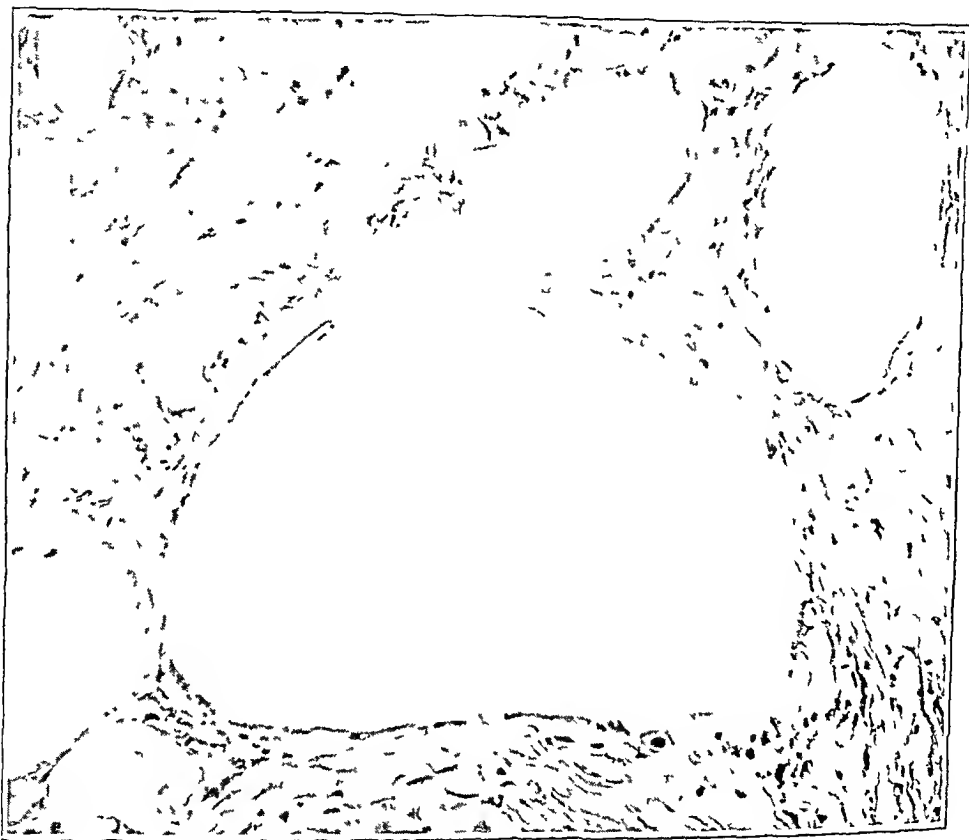


Fig. 8.—Large fat cyst with syncytial lining

turbance, they all act in the same way—they injure or destroy the fat cells. According to Makai, the injured fat tissue is susceptible to the effect of the lipase, the existence of which in the subcutaneous fat tissue has been demonstrated by experimental work. When liberated from injured fat tissue, this lipase leads to the decomposition of the fat whereby fatty acids and other lipoid materials are liberated. These

4. Stuebler: *Virchows Arch. f. path. Anat.* **247**:159, 1923.

5. Schottlaender: *Arch. f. Gynäk.* **78**:137, 1906

6. Gentili: *Arch. f. Gynäk.* **77**:616, 1905.

substances act as foreign bodies and stimulate the formation of giant cells (Berner,⁷ Heyde,⁸ Farr,⁹ Knappe,¹⁰ von Gierke¹¹ and Askanazy.¹²

The close resemblance of the necrotic foci in the fat tissue to fat necrosis of the pancreas has suggested the possibility that pancreatic lipase may be the acting enzyme. However, von Gierke's experiments have shown that such changes also occur *in vitro* without the possibility of pancreatic interference.

In view of the frequency with which impairment of the subcutaneous fat tissue ought to and does occur, it seems peculiar that lipogranulomatosis is not more common. Since attention has been called to the existence of these lesions, they have been found more frequently than in the past, yet their frequency remains much below that of causes likely to elicit these changes. This consideration induced Makai to suggest a constitutional factor that may possibly depend on endocrine influences. Similar views were also suggested by Brancati. It has been reported that the administration of thyroid has a beneficial effect on such lesions (Bessau¹³), and in one of Makai's cases cod liver oil also gave favorable therapeutic results. At present the endocrine concept seems so hypothetic that its discussion is hardly warranted before the accumulation of further facts. However, it seems of importance, as Makai emphasized, that the healing of wounds in these patients is often prolonged and yields massive, ugly scars in spite of primary union. This observation strengthens suspicion that some constitutional factor is at play. The frequent multiplicity of the lesion and its tendency to recur, as observed in case 2, also point in the same direction.

In reviewing the literature, a number of references are available to show that lipogranulomatosis may occur in any part of the body that harbors fat tissue. From the surgeon's point of view, perhaps the greatest importance might be attached to the lipogranuloma that arises in the glands of the breast. Such observations were recorded by Targett,¹⁴ Lanz¹⁵ and Berner,⁷ but their clinical significance was not properly stressed before the publication of the paper of Lee and Adair,¹⁶ and particularly that of Hadfield.¹⁷ The latter author collected forty-two cases on record under the heading of "fat necrosis of the breast."

7. Berner: *Virchows Arch. f. path. Anat.* **187**:360, 1907; **193**:510, 1908.

8. Heyde: *Deutsche Ztschr. f. Chir.* **109**:500, 1911.

9. Farr, R. E.: *Ann. Surg.* **80**:670, 1924.

10. Knappe: *Virchows Arch. f. path. Anat.* **207**:321, 1912.

11. von Gierke: *Verhandl. d. deutsch. path. Gesellsch.* **15**:433, 1912.

12. Askanazy, M., and Jentzer, A.: *Wien. med. Wchnschr.* **79**:3, 1929.

13. Bessau, G.: *Monatschr. f. Kinderh.* **38**:438, 1928.

14. Targett: *Tr. Path. Soc., London* **47**:249, 1896.

15. Lanz: *Zentralbl. f. Chir.* **25**:1253, 1898.

16. Lee, B. J., and Adair, F. E.: *Ann. Surg.* **80**:670, 1924.

17. Hadfield, G.: *Brit. J. Surg.* **17**:673, 1930.

Other recent contributions on this subject are the papers of Gohrbandt,¹⁸ Trnica,¹⁹ Wellbrock²⁰ and Brancati.²¹ Most of these authors emphasized the clinical resemblance of these lesions to early carcinoma. The differential diagnosis is often established only by histologic examination. It is far easier, however, to confuse the lesion of the breast with tuberculosis, and I feel inclined to believe that more than incidental diagnostic mistakes of this kind have been committed.

The most common seat of the lesion is the subcutaneous fat tissue, and the majority of the cases on record show this localization (Heyde,⁸ Kuettner,²² Moir,²³ Schujeminoff,³ Kedrovsky,³ Schamow,²⁴ Abrikossoff,² Makai,¹ Alexander,²⁵ Strasser²⁶ and others). In some cases the direct relationship to trauma was well established, as in case 1; in others, the perivascular infiltration of the subcutaneous tissue in typhus (Schujeminoff³) or the vocational injuries of the skin in working men (Kogan Jasny²⁷) could be blamed. Their apparently frequent occurrence in amputational stumps has been noticed only recently (zur Verth,²⁸ Makai²⁹ and Protopow³⁰) and seems to deserve the attention of the surgeon.

Lipomas are another comparatively frequent seat of lipogranuloma, as was known to Virchow. Targett,¹⁴ Shattock,³¹ Knape,¹⁰ von Gierke¹¹ and others describe lipomas with secondary lipogranulomatous changes, usually of the calcifying type. Calcification, however, may also develop in single or multiple subcutaneous lesions (Chiari,³² Huebschmann,³³ Lanz¹⁵ and others) or may be widely scattered, as in Schamow's²⁴ remarkable case of "interstitial calcinosis."

Lipogranuloma occasionally develops in other parts of the body, such as the mesentery, retroperitoneal fat tissue and bone marrow. The immediate cause is always injury to the fat tissue, such as is produced by an invading tumor. A considerable number of observations have

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18. Gohrbandt, P.: *Arch. f. klin. Chir.* **148**:684, 1927.
 19. Trnica: *J. Coll. Surgeons, Australasia* **2**:21, 1929.
 20. Wellbrock, W. L. A.: *Ann. Surg.* **90**:154, 1929.
 21. Brancati, R.: *Arch. ital. di chir.* **26**:585, 1930.
 22. Kuettner: *Berl. klin. Wchnschr.* **1**:9, 1913.
 23. Moir, P. J.: *Brit. M. J.* **1**:64, 1929.
 24. Schamow: *Zentralbl. f. Chir.* **51**:2221, 1924.
 25. Alexander, A.: *Klin. Wchnschr.* **8**:2138, 1929.
 26. Strasser, U.: *Klin. Wchnschr.* **9**:987, 1930.
 27. Kogan Jasny: *Ztl. Org. Chir.* **39**:265, 1927.
 28. zur Verth, M.: *Arch. f. klin. Chir.* **157**:55, 1929.
 29. Makai, E.: *Zentralbl. f. Chir.* **57**:590, 1930.
 30. Protopow: *Zentralbl. f. Chir.* **57**:206, 1930.
 31. Shattock: *Tr. Path. Soc., London* **47**:246, 1896.
 32. Chiari: *Ztschr. f. Heilk.* 1908, Suppl. quoted from v. Gierke.
 33. Huebschmann: *München. med. Wchnschr.* **72**:1579, 1925.

recently appeared which call attention to the appearance of "granulation tissue with foreign body giant cells," i. e., lipogranuloma in fat tissue invaded by malignant growth (Fleischmann,³⁴ Gohrbandt,¹⁸ Petri,³⁵ Teutschlaender,³⁶ Wellbrock²⁰ and others).

Pediatricians particularly have been puzzled by the peculiar changes of the subcutaneous fat tissue in scleroderma of the new-born (Bernheim-Karrer³⁷) or subcutaneous fat necrosis with or without calcification (Farr,⁹ Bessau,¹³ Pozzo and Bianchi,³⁸ Heubschmann³³ and others). A more complete survey of the literature dealing with this particular phase of the subject can be gathered from the paper of Epstein and Barash,³⁹ who have discussed the question 'from the point of view of the pediatrician.

Finally, the dermatologists have paid considerable attention to lesions of a similar nature (Schwarzmann,⁴⁰ Lecène and Moulounguet,⁴¹ Alexander²⁵ and others); yet, as pointed out by Makai and Abrikossoff, it seems that increasing knowledge of lipogranulomatosis may change some of the concepts concerning certain conditions of the skin, such as Darier's sarcoid, Bazin's indurating erythema and the various types of lesions summarized as tuberculids. It seems probable that toxic lesions or allergic reactions of the subcutaneous fat tissue account for the injury of fat cells which is followed by the development of the nonspecific lipogranuloma. When one looks at these lesions as reactions specific to fat tissue but nonspecific as far as the eliciting cause is concerned, one may attain a more satisfactory interpretation of tuberculids and allied changes.

It stands to reason that any disease that occurs in so many places of the body and in connection with such varied conditions is likely to be more or less misunderstood, particularly if its morphologic aspects also show variations over a wide range. It therefore seems of definite value to establish a common basis for these varied conditions expressed by a unification of nomenclature. The various names proposed in the literature, such as fat necrosis of the breast, fat stone, oleogranuloma, calcinosis interstitialis, cystic lymphangitis, chalazion (Schall⁴²) and the various dermatologic terms each express but one phase in the devel-

34. Fleischmann, R.: *Arch. f. klin. Chir.* **158**:692, 1930.

35. Petri: *Zentralbl. f. Path.* **37**:1, 1926.

36. Teutschlaender, O.: *Frankfurt. Ztschr. f. Path.* **35**:436, 1927.

37. Bernheim-Karrer: *Ztschr. f. Kinderh.* **42**:658, 1926.

38. Pozzo, F., and Bianchi, A. E.: *Arch. de méd. d. enf.* **30**:529, 1927.

39. Epstein, J., and Barash, L.: *Subcutaneous Fat Necrosis*, *Am. J. Dis. Child.* **40**:337 (Aug.) 1930.

40. Schwarzmann, J. M.: *Ann. de dermat. et syph.* **1**:476, 1930.

41. Lecène, P., and Moulounguet, P.: *Ann. d'anat. path.* **2**:193, 1925.

42. Schall, E.: *Arch. f. Ophth.* **117**:662, 1926.

opment of the lesion or some peculiarity due to its localization. Makai deserves the credit for having opened the field for unified consideration of these varied but pathogenically identical changes. The name lipogranuloma expresses properly the histogenesis and character of the lesion. Its frequent occurrence in multiple, sometimes symmetric, foci (Strasser ²⁶) justifies the term lipogranulomatosis, which also includes reference to the possible constitutional factors.

SUMMARY

Three cases of lipogranulomatosis are described, two in the subcutaneous fat tissue and one in the breast. The histogenesis of the lesion is discussed, and its frequency and clinical importance are emphasized.

THE NATURE OF LIVING CELLS

WITH SPECIAL REFERENCE TO THE NATURE OF CANCER
CELLS AND OF FATTY DEGENERATION *

GEORGE W. CRILE, M.D.

MARIA TELKES, PH.D.

AND

AMY F. ROWLAND, M.A.

CLEVELAND

The research a preliminary report of which is here presented was undertaken with the purpose of discovering some physical principle that might account for the conversion of normal cells into cancer cells, that is, into cells the energy of which is used only for growth, whereas the energy of the tissue in which the conversion takes place is used primarily for function. It is clear that the cancer cell must owe its formation to the operation of existing laws of growth in the host. These laws are most strikingly illustrated in the process of fertilization.

The ovum and the sperm, as Keller has shown, exhibit opposite signs of charge, hence they attract each other. The preponderantly positive element exists apart from the preponderantly negative element, but when they unite growth and division take place, forming the beginning of a new organism. The fertilized ovum contains, therefore, elements bearing opposite signs of charge and electrolytes in optimum proportions, and transmits these characteristics to each cell of the developing organism.

Every living cell contains proteins, lipoids and electrolytes. Colloidal systems of proteins and of lipoids bear different degrees of electrical charge. We postulated, therefore, that if we were to mix proteins and lipoids with the electrolytes present in living tissues, the same laws would act that govern the process of fertilization; that is, that the comparatively positive element would combine with the comparatively negative element, this combination with the electrolytes carrying an electric charge and forming an organized unit which would present a cell-like form. In other words, we proposed to test by experiment whether or not after the essential fractions of the cells of an animal had been separated they could be reassembled to form a lower undifferentiated type of cell that would bear a certain physical resemblance to the cell from which the material of which it was made was derived, and would also exhibit some of the phenomena of the parent cells.

* Submitted for publication, Jan. 27, 1931.

* From the Cleveland Clinic Foundation.

This research is by no means the first attempt to produce artificial cells. Such cells have been formed from inorganic and organic material by many investigators, notably Beutner, Butschli, Herrera, Le Duc, Lehmann, Loeb and MacDougal. The cells formed by these investigators have shown such phenomena as division, nucleation, growth and ameboid movement, but in cells made by their formulas, respiration, repeated division and prolonged exhibition of the manifested phenomena have not been observed. The cells of MacDougal showed a difference in ion concentration analogous to biologic cells. The investigations of Bastian and others are of a different type.

As we have stated, it has been our hope that from the study of undifferentiated cells made up of proteins, lipoids and electrolytes extracted from tissues, we might ultimately gain some insight into the processes whereby malignant cells are formed from the proteins, lipoids and electrolytes of their parent tissues.

To these cells thus formed from proteins, lipoids and electrolytes we have applied the term *autosynthetic cells*. We expected that, because of the potential differences between the elements from which they were synthesized, these *autosynthetic cells* would themselves carry an electric charge and would show growth energy; that they would divide, would have respiration and would show motility. The extent to which our expectations have been realized is stated in the following summary of experiments.

EXPERIMENTAL OBSERVATIONS

From the organs of freshly killed normal animals, the lipoids and proteins of the brain were extracted and the ash was obtained. By mixing the lipoids and the proteins of the brain and a solution of the brain ash or of the electrolytes contained in the brain, the process of fertilization in nature by the uniting of the spermatozoon and the ovum was imitated.

On observation of this mixture of lipoids and proteins of the brain and the solution of electrolytes under the microscope, we noted immediate activity of organization. Cell-like forms appeared and grew slowly (fig. 1). They multiplied, sometimes by budding, and sometimes by direct division (fig. 2). These cells were nucleated; they took vital stains; they consumed oxygen; they gave off carbon dioxide. Under a high power lens, free movement of granules and a movement not unlike the brownian movement were seen, and sometimes the movement was so rapid that it was difficult to keep the cells in the field of vision of the microscope. Some of these mixtures have continued to show active cells for two and one-half months.

Exactly the same technic was carried out for the other organs of animals. The lipoids and proteins of the various organs other than the

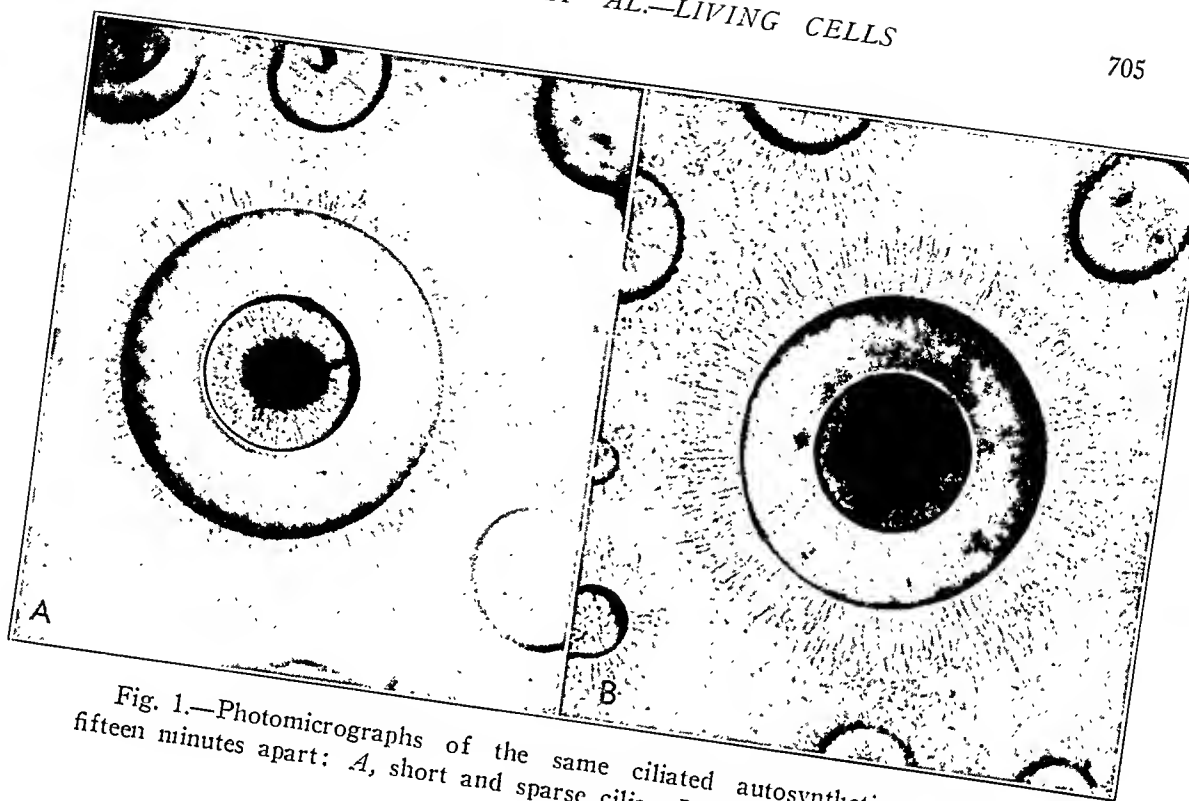


Fig. 1.—Photomicrographs of the same ciliated autotrophic cell taken fifteen minutes apart: *A*, short and sparse cilia; *B*, long and abundant cilia.

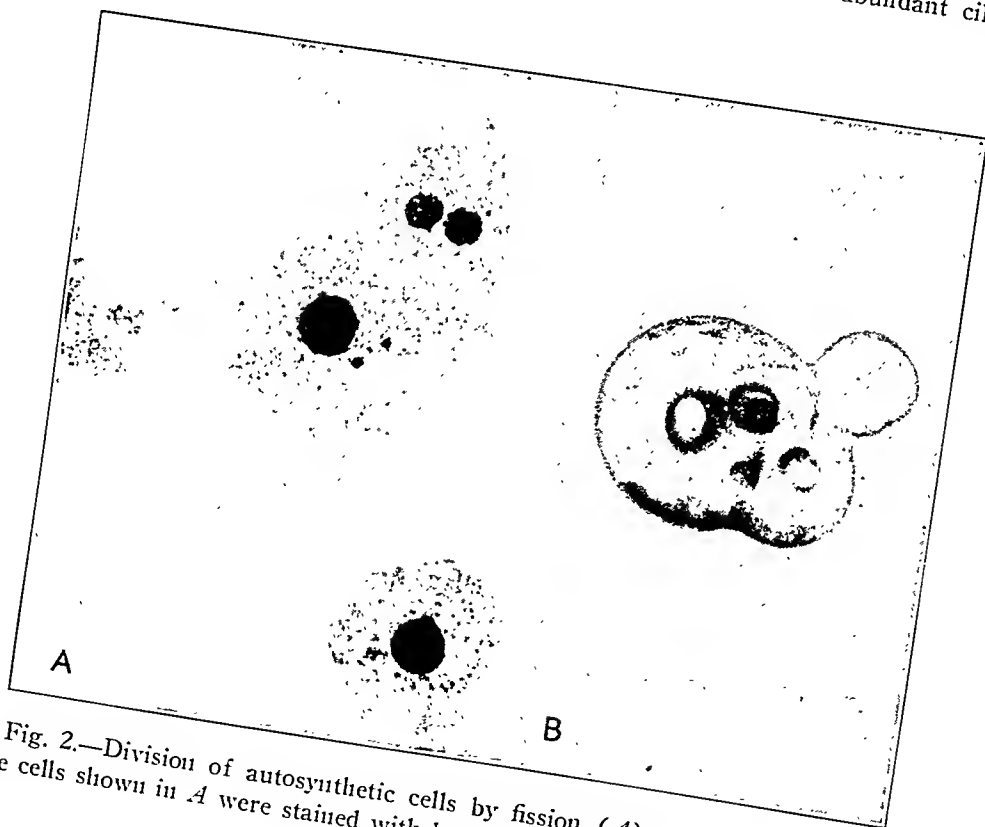


Fig. 2.—Division of autotrophic cells by fission (*A*) and by budding (*B*). The cells shown in *A* were stained with hematoxylin-eosin.

brain were extracted and the ash was obtained; but on mixing the lipoids, proteins and a solution of the ash of these various organs, only feeble or no power of organization was seen. The nearest approach to organization in extracts from organs other than the brain was in the case of the spleen, and to a lesser degree of the ovary and the testes, but

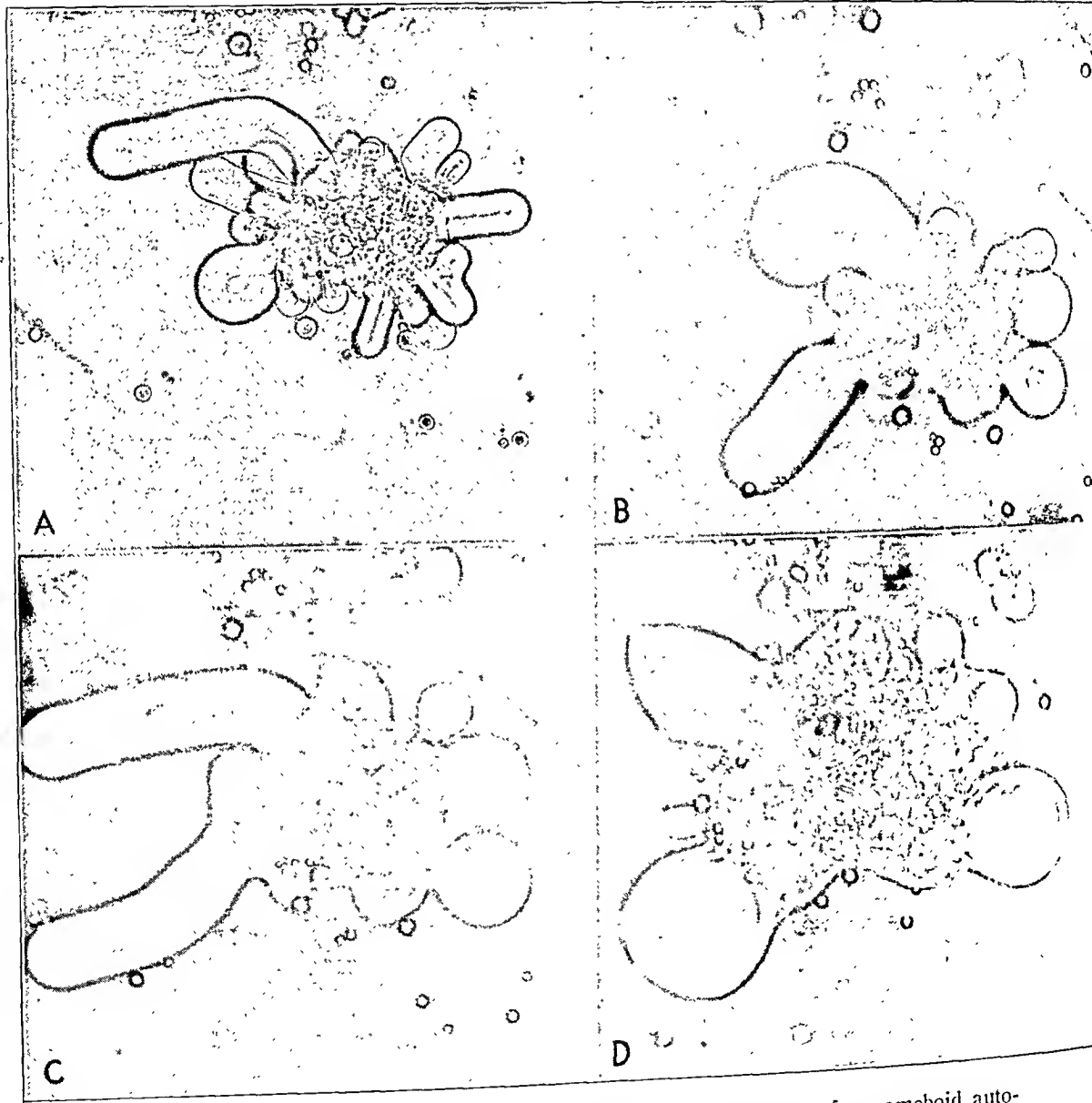


Fig. 3.—Successive stages in the growth and movement of an ameboid auto-synthetic cell. Forty-eight photomicrographs of this cell were taken at intervals of fifteen minutes. The photomicrographs shown here were taken at the following intervals after *A*: *B*, one hour and forty-five minutes; *C*, four hours and forty-five minutes; *D*, eleven hours and thirty minutes.

the organization seen in these cases was not at all of the same order as that which took place in the mixture of the elements of the brain.

We next observed the effects of adding the lipoids of the brain to the proteins and solutions of the ash of each of the other organs. Immediate organization was observed. The cell-like structures that were

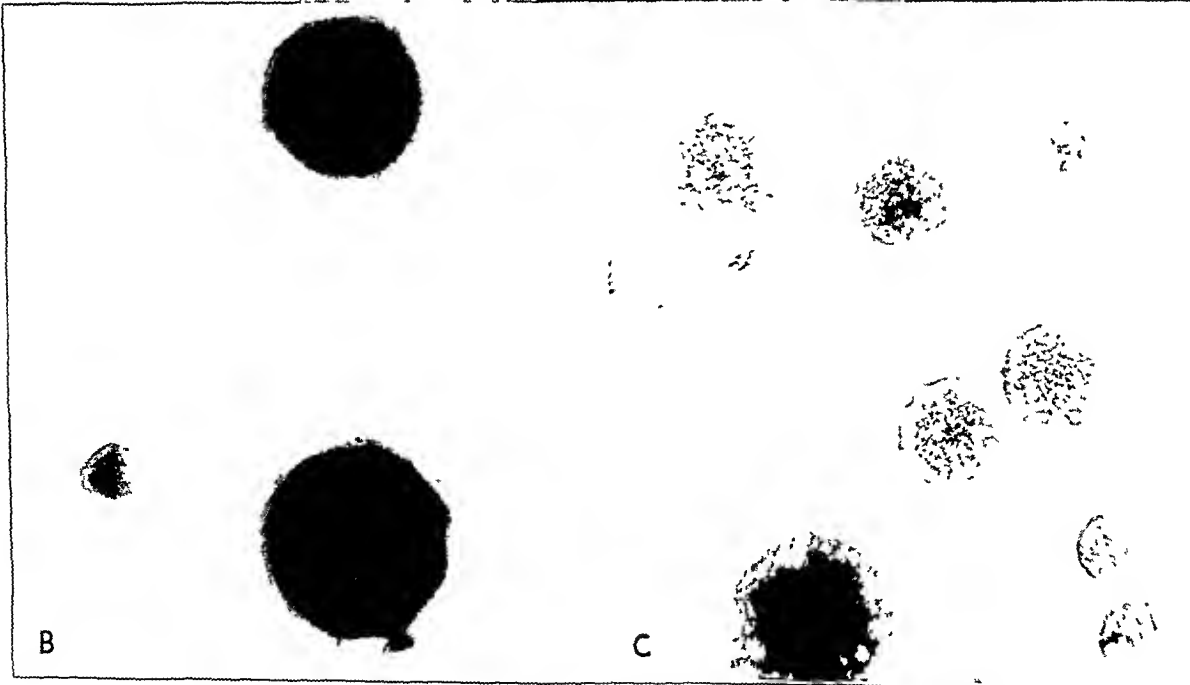


Fig. 4.—The effect of exhaustion on the formation of autosynthetic cells: *A*, normal autosynthetic cells; *B* and *C*, unorganized masses produced in the mixture of protein and electrolyte solution with *B* the lipid extracted from the brain of a rabbit that died of exhaustion from insomnia, and (*C*) the lipid extracted from the brain of a dog that had died from distemper.

formed took vital stains; they grew in size; they multiplied and showed respiration. This experiment revealed clearly that the lipoid of the brain is unique in being the possessor of a structure that has the power of organizing the proteins of any organ.

As we have stated, these autotrophic cells took vital stains (fig. 2*A*). They grew and multiplied. They showed internal organization such as a nucleus, granules, etc. They varied considerably in size. They had respiration, their consumption of oxygen running as high as 14 mm.³ per hour per 2 cc. of cell mixture over a period of five hours, the respiratory quotient ranging from 0.7 to 0.98. Some of these cells were obtained for a period of nine hours, and many

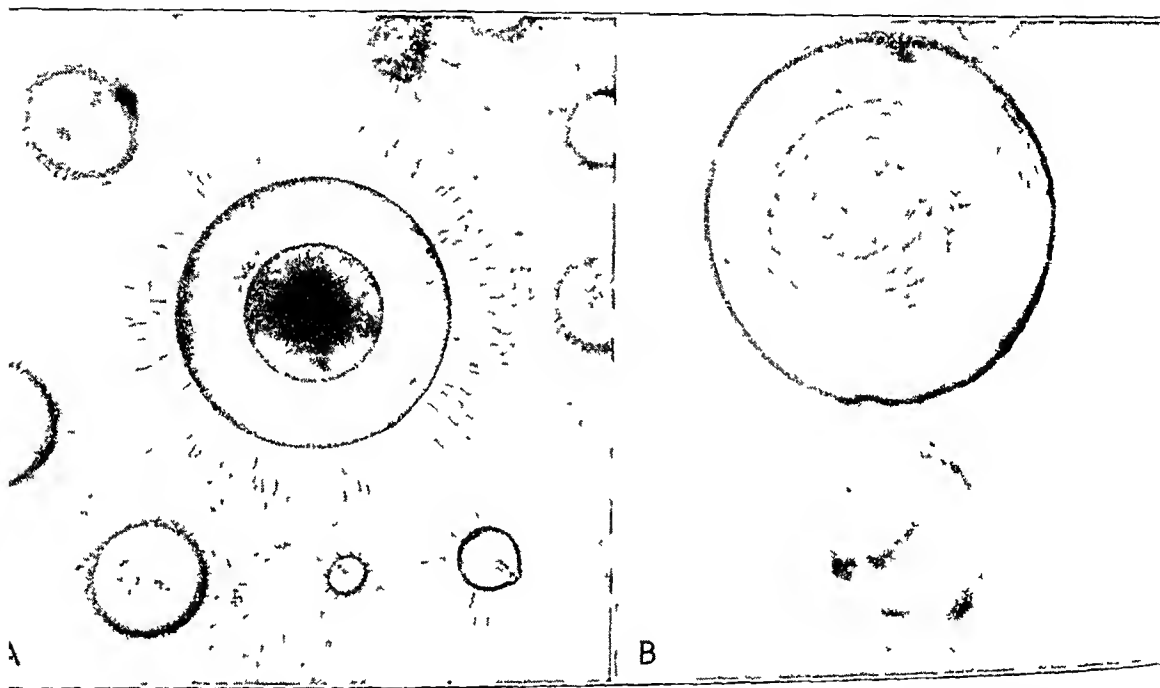


Fig. 5—The effect of radiation on autotrophic cells. *A*, normal autotrophic cell; *B*, radiated autotrophic cells. Note the unorganized masses of fat within the cell membranes.

photographs showing the changes in their form were taken. The form of the cells seemed to depend on the p_H of the electrolyte solution, ciliated cells being always produced in a solution of p_H 7.5.

While carrying out the effects of adding various "food" substances to the cells, it was found that dextrose increased the metabolism of the cells while the various culture materials such as beef broth, agar, blood serum, etc. showed little or no effect. It is necessary, however, in order to keep cultures alive over a period of time, to feed them by the occasional addition of protein. In one case suprarenal protein was added, and the cell immediately assumed the appearance of an amoeba and pseudopodia like those of an active amoeba were thrust out. Occa-

sionally the cell moved, apparently without first thrusting out pseudopodia, although the usual manner of movement was by the thrusting out of a loop of fiber-like substance from the body of the organism, into which loop the contents of the organism, the granules, etc., seemed to flow, the organism moving in the direction of the flow (fig. 3).

Of special significance was our observation that autotrophic cells were not formed in the brain-lipoid-brain-protein, electrolyte mixture of dogs which had died from distemper. In rabbits that had died of exhaustion from insomnia, unorganized masses appeared in a mixture of this kind (fig. 4).

On the addition to the brain lipoids and proteins of an electrolytic solution identical with the brain ash solution, with the exception

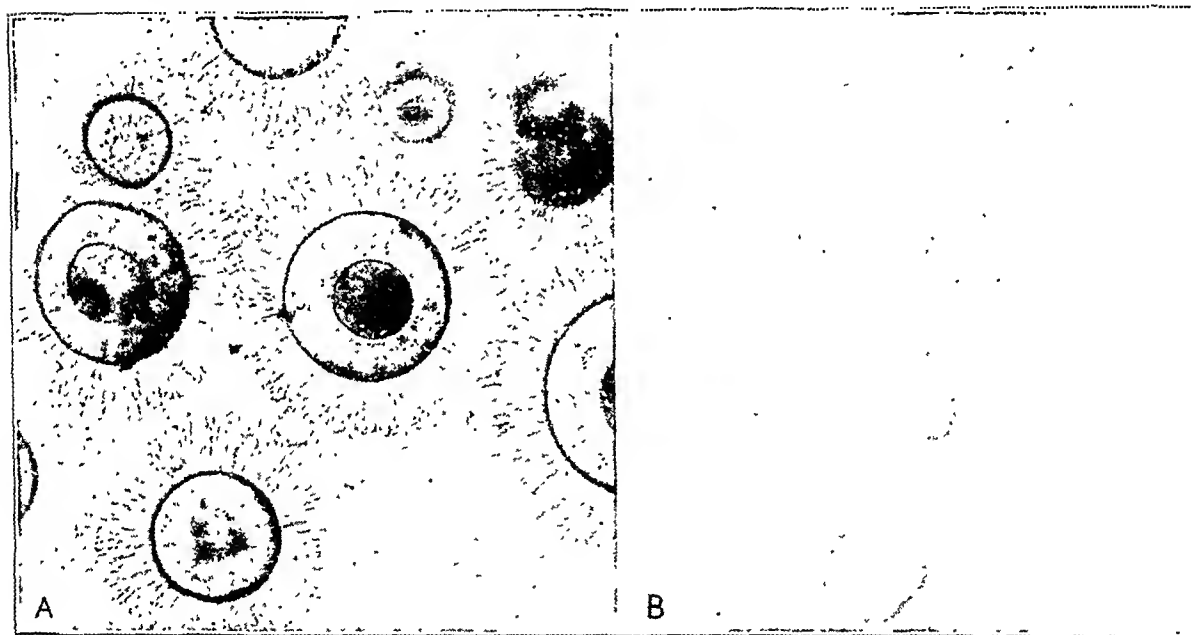


Fig. 6.—The effect of lack of oxygen (asphyxiation) on the production of autotrophic cells: *A*, normal autotrophic cells; *B*, lack of organization and fatty droplets in a mixture of electrolyte solution and protein with lipoids which had been shut away from the air for a number of weeks.

that the potassium salt was omitted, the formation of cells was delayed, and the cells differed in form from those found in the complete brain ash solution. It should be noted that the lipoids themselves held adsorbed potassium ions. Could all the potassium be eliminated, it might be that the organization of cells would be entirely inhibited.

In collaboration with Dr. Otto Glasser of the Cleveland Clinic Radiation Research Laboratory, we subjected the lipoids of the brain to intense radiation before they were mixed with the proteins of the brain and the electrolyte solution, and we found that the mixture had lost the power of organization—no cells were formed. The radiated lipoid

Cataphoretic measurements have been made from which the electric charge of the protein, of the lipid and of the structures have been calculated. There was a marked potential difference between the lipid and the protein, and the charge on the cells has been found to vary from 50 to 70 millivolts.

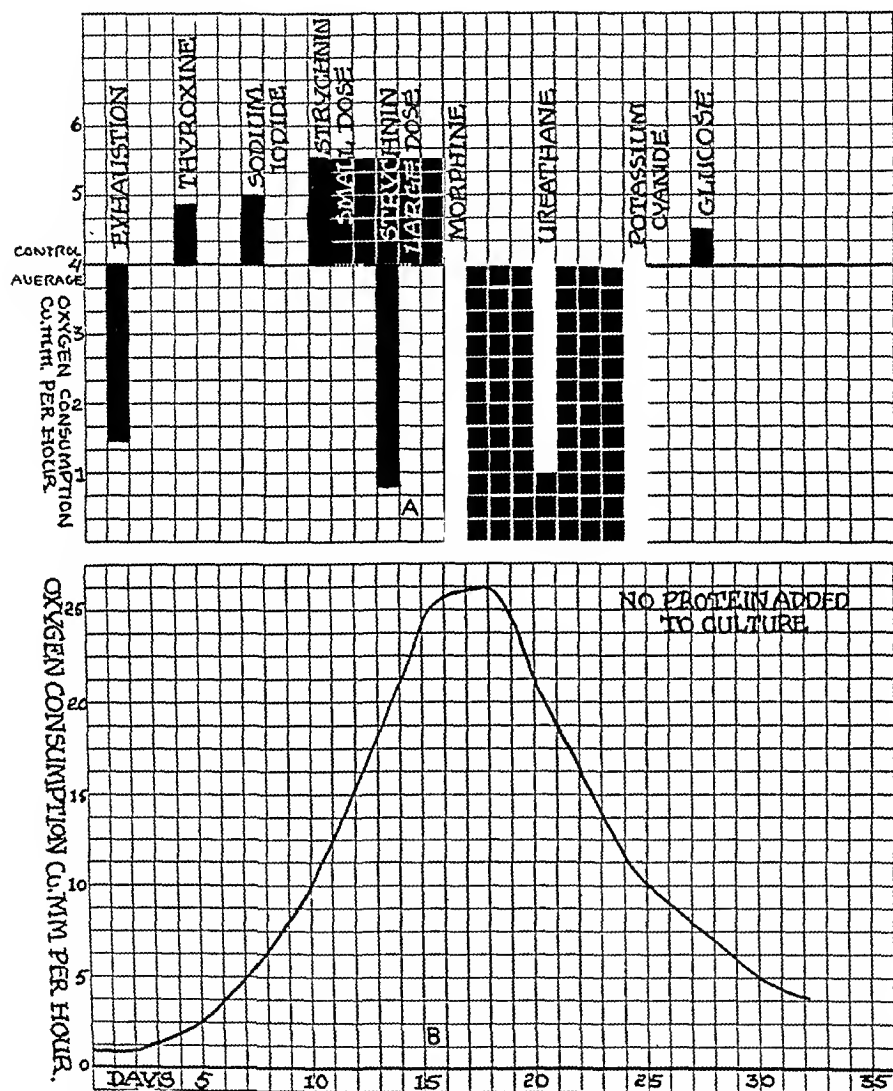


Fig. 8.—The oxygen consumption of autotrophic cells: *A*, The effect of various agents on the oxygen consumption of autotrophic cells; *B*, The progressive changes in the oxygen consumption of autotrophic cells during thirty-four days.

Direct measurements of the electric potential difference of the cells and of the nucleus and cytoplasm were made by introducing electrodes into them. The nucleus was found always to be positive with relation to the cytoplasm, the difference of potential varying between 20 and 30 millivolts.

When "old lipoids," that is, when lipid material that had been kept over a number of weeks and had been shut away from the air was used, we observed that instead of organized autotrophic cells, fatty droplets were formed (fig. 6). These fatty droplets which were similar to those seen after the lipid had been radiated were seen also after a cyanide was

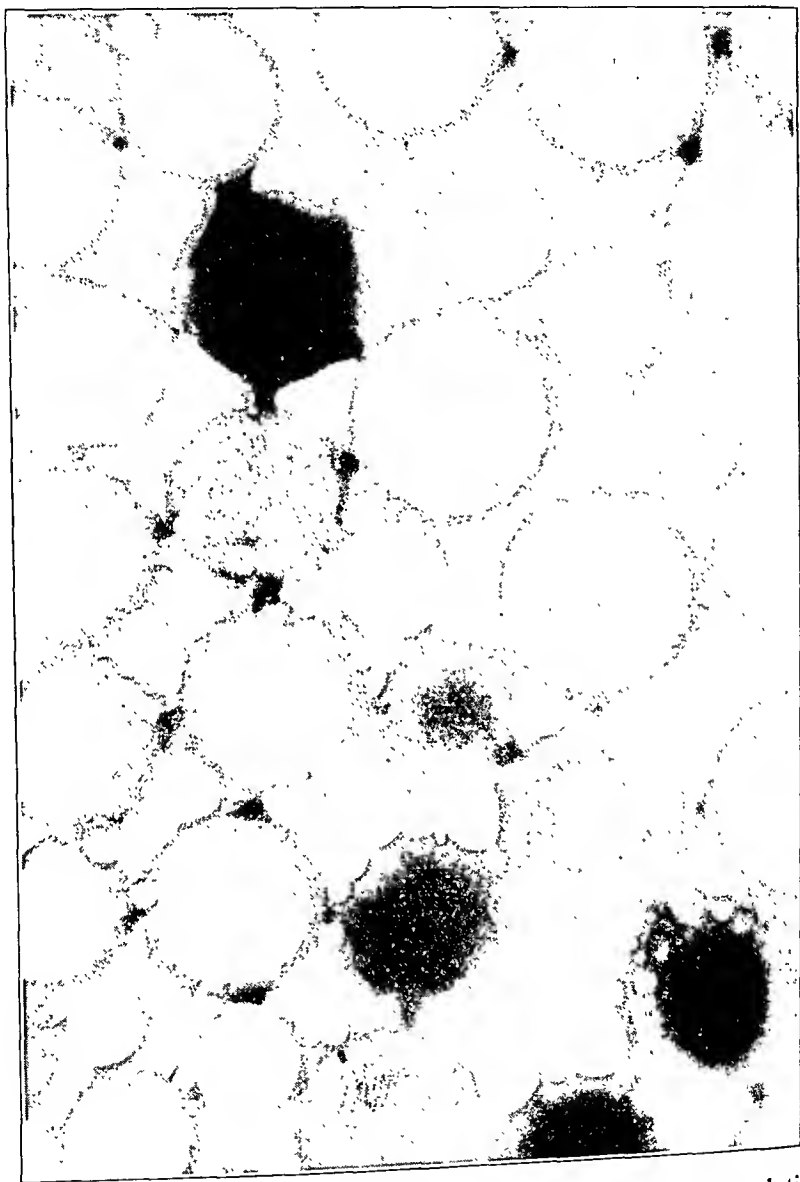


Fig. 9.—Unorganized masses produced in a mixture of electrolyte solution with the lipid and protein extracted from a cancer.

added to the lipid mixture and after the structures were deprived of oxygen, that is, asphyxiated. The phenomenon apparently corresponds to fatty degeneration.

The effects of the addition of various agents to the mixture of lipid, protein and electrolyte were as follows: Both the potential difference

and the respiration were decreased on the addition of an anesthetic (urethan) (figs. 7 and 8). (Note: The effect of ether and of chloroform could not be tested as they immediately dissolved the lipoid.) The addition of salts in various concentrations affected the potential difference of our autosynthetic cells in a manner strikingly similar to the effect of the same concentrations on the potential differences of bacteria (Brown and

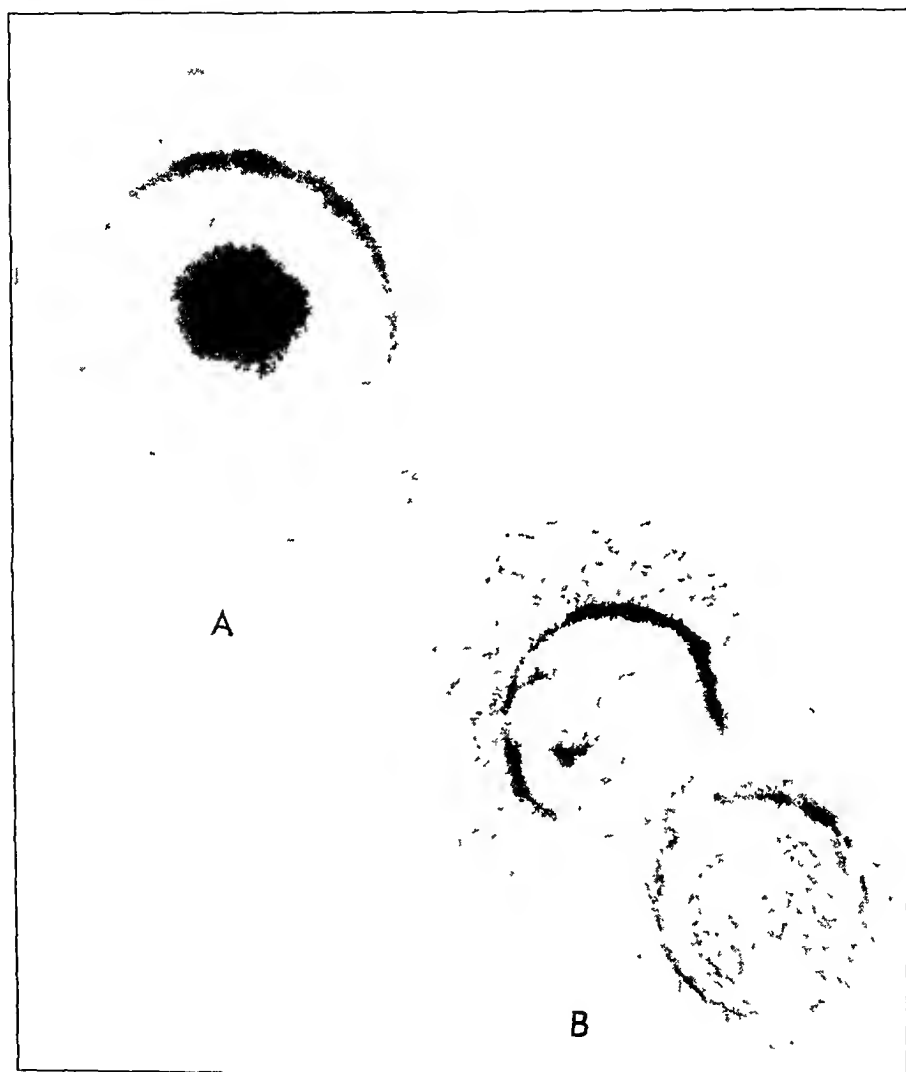


Fig. 10—Autosynthetic cells produced in a mixture of electrolyte solution with the lipoids and proteins extracted from a human brain. Note the active division in progress in (B).

Broom) as is shown by the plotted curves in the chart. Both the potential difference and the respiration of the autosynthetic cells were increased on the addition of some agents. The potential difference and the respiration were decreased on the addition of morphine. On the addition of a small amount of strychnine or of alcohol (from 3 to 5 per cent), the

potential difference was increased. On the addition of large amounts of either strychnine or alcohol (50 per cent), the potential difference was decreased. On the addition of a cyanide or of a toxin, the potential difference was decreased to zero.

The lipoids and proteins extracted from a cancer, when mixed with a solution of the ash of the same cancer, did not produce cells; but a bizarre structure characterized by the appearance of many fatty droplets (fig. 9).

A mixture of the lipoids and proteins of a human brain with the electrolyte solution produced a highly organized cell with active division (fig. 10).

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INTRACAPSULAR FRACTURES OF THE NECK OF THE FEMUR

TREATMENT BY INTERNAL FIXATION *

M. N. SMITH-PETERSEN, M.D.

EDWIN F. CAVE, M.D.

AND

GEORGE W. VANGORDER, M.D.

BOSTON

Nails of various types, either round or square, have been used for internal fixation of intracapsular fractures of the neck of the femur with varying success. This type of treatment has been abandoned because it brought about partial and temporary fixation only. Since the fixation was only partial, immobilization by means of a plaster cast had to be superimposed on the open operation until repair was far enough advanced to stand the strain of function. Since early function is the most important principle in the treatment of any joint fracture, this type of treatment necessarily fell short of the ideal. The type of nail previously used brought about temporary fixation only. This was due to the fact that the nail was massive; it displaced so much bone that it actually created pressure necrosis surrounding it. Due to this necrosis, within a short time the nail became loose and ceased to function.

To eliminate these two weak points a flanged nail was devised (fig. 1) which brought about absolute fixation in all directions and displaced a minimum amount of bone. Because of its flanges, the nail is gripped by the cortex of the bone so that there can be no rotation; because of its shape, the surface area is much greater than that of the ordinary nail and friction is proportionately increased; because of the minimum displacement of bone, there is less pressure necrosis surrounding it; consequently, the fixation is sustained and complete, not temporary and partial.

OPERATIVE TECHNIC

A great responsibility rests on the surgeon who introduces a new method of treatment. The desire to have a new idea published is so great that the originator is often led astray, and the method is broadcast before it has been proved worthwhile and before the technic has been perfected. The method that is the subject of

* Submitted for publication, Oct. 15, 1930.

* From the Fracture Service of the Massachusetts General Hospital.

this paper has been used for five years, and a sufficient series of cases has been studied to prove that it is worthwhile; the technic has been developed, and many errors eliminated.

The success of any operation for open reduction of a joint fracture depends on the exposure of that fracture and the ease with which the surgeon can accurately align the fragments. At first, two incisions were used. These adequately exposed the fracture but made it difficult to aim the nail accurately. To eliminate this

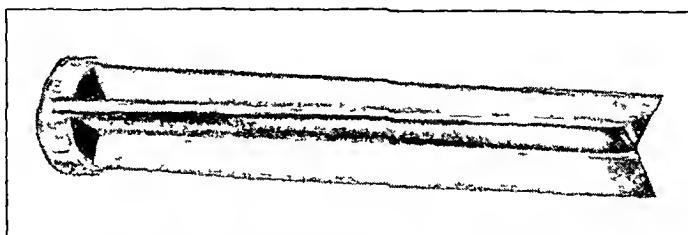


Fig. 1.—Flanged nail used in operation.

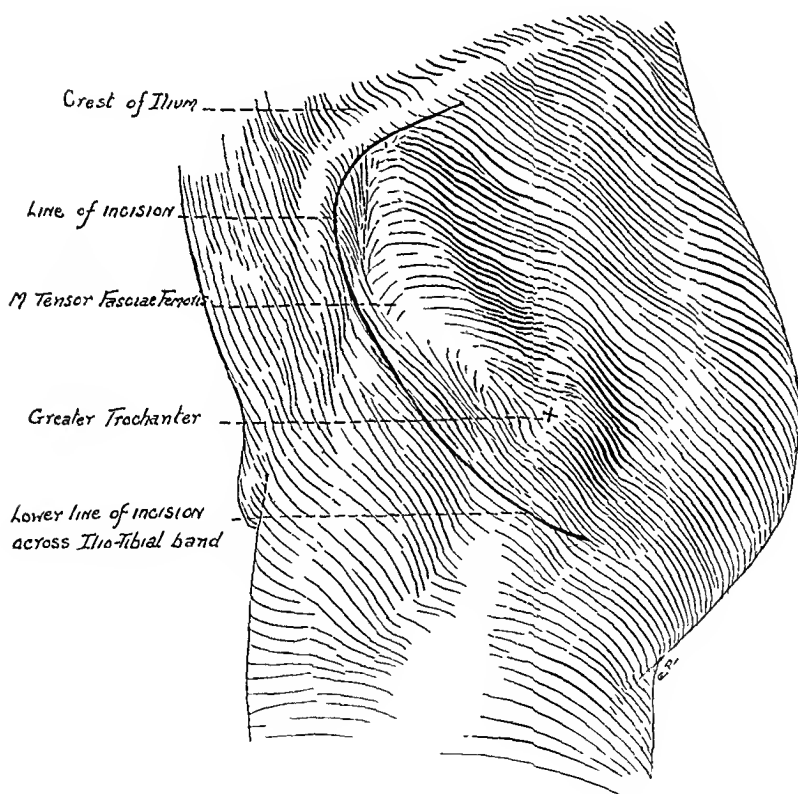


Fig. 2.—Incision used in operation.

difficulty, one incision, a more extensive one, was developed (fig. 2). This is a modification of the incision previously described by one of the authors (Dr. Smith-Petersen).¹

The skin incision is made along the anterior third of the crest of the ilium, and continued along the anterior border of the tensor fascia femoris, curving posteriorly across the insertion of this muscle into the iliotibial band in the subtrochanteric

1. Smith-Petersen, M. N.: New Approach to Hip Joint, *Am. J. Orthop Surg.* **15**:592 (Aug.) 1917.

region. It should be kept in mind that the insertion of the tensor fascia femoris into the iliotibial band is low, from 3 to 4 inches below the base of the trochanter. The line of incision of the fascia (fig. 3) follows the anterior border of the tensor fascia femoris. Care should be taken not to injure the anterior femoral cutaneous nerve; it is mesial to the inner border of the tensor fascia femoris, close to the lateral border of the sartorius.

The muscle attachments to the lateral aspect of the ilium are now incised along the crest of the ilium. It is important to make this a clearcut incision down to the bone, through the periosteum, since it then becomes easy to make a true periosteal

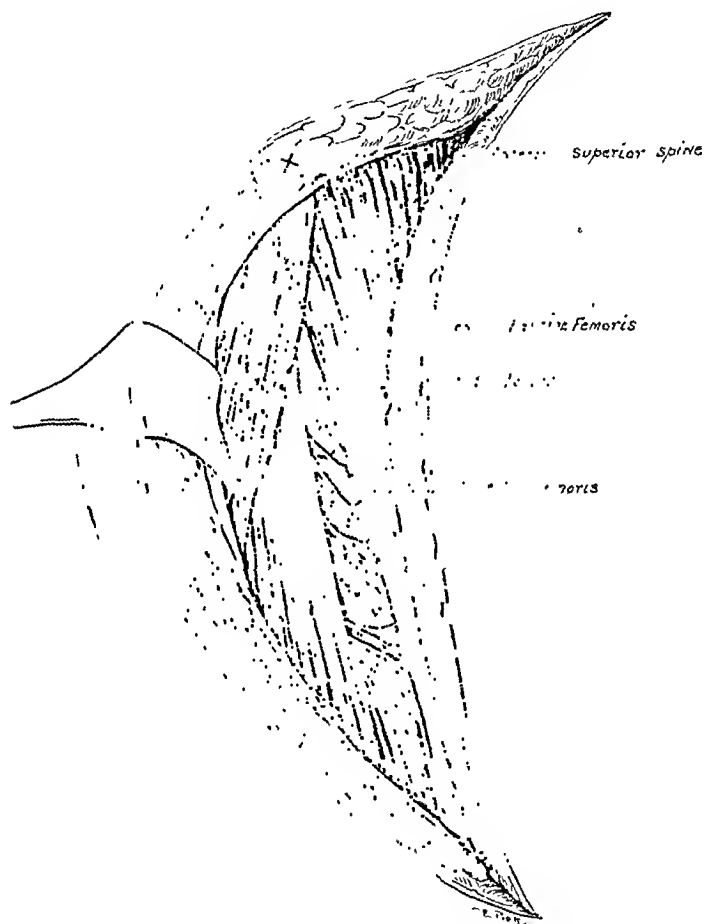


Fig. 3.—Line of incision of the fascia.

reflection. The periosteum reflects easily as a continuous structure—it should not be frayed. The periosteum is reflected down to the superior margin of the acetabulum, and the muscle attachments between the anterior superior spine and the cotyloid ligament are divided. The flap thus reflected consists of the tensor fascia femoris, the gluteus minimus and the anterior portion of the gluteus medius. Inferiorly, the fascial incision is carried across the insertion of the tensor fascia femoris into the iliotibial band, exposing the superior portion of the rectus and the anterior portion of the vastus lateralis.

The capsular incision is again a flap incision (fig. 4). It starts at a point just lateral to the cotyloid ligament, over the inferior aspect of the capsule. From this

point, it extends parallel with the cotyloid ligament to the superior aspect of the capsule. It then curves laterally and continues beyond the capsule to the base of the greater trochanter. It will be noticed that this incision divides a portion of the reflected head of the rectus femoris, which blends with the capsule below its insertion into the superior margin of the acetabulum; by reflecting it with the capsule, the capsular flap becomes stronger and repair consequently easier. It also gives a continuous exposure of the anterior aspect of the hip from the cotyloid ligament to the base of the trochanter (fig. 5).

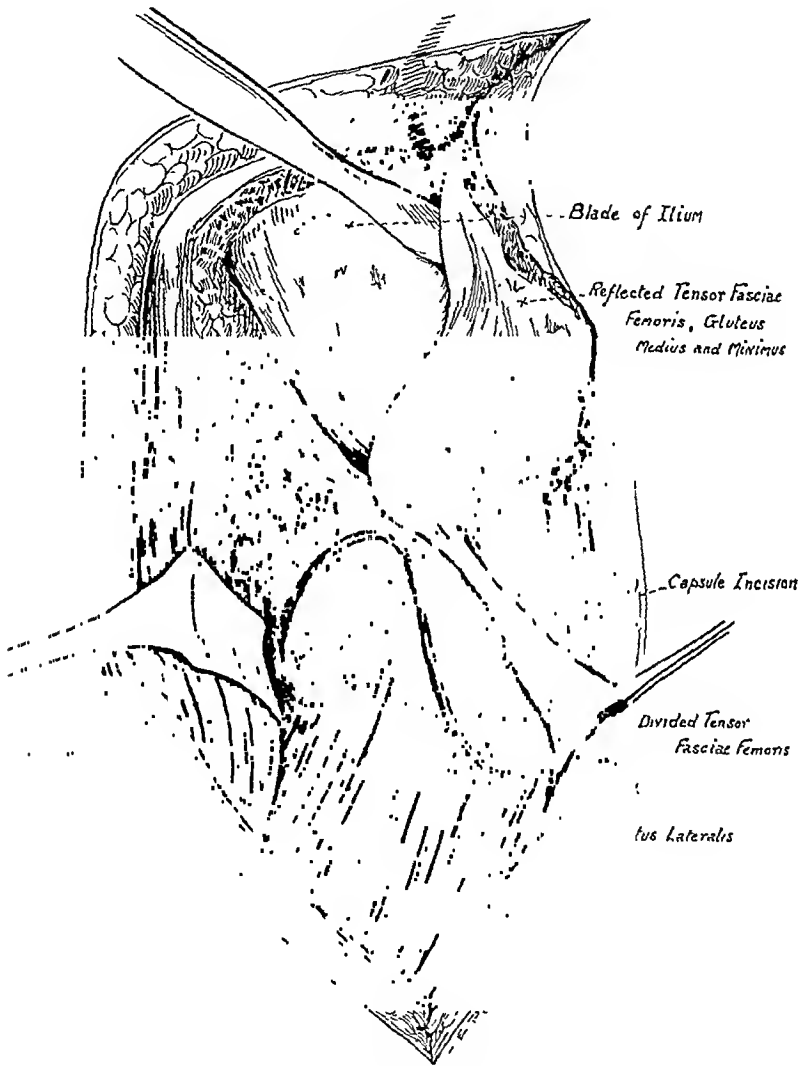


Fig. 4.—Capsular incision.

The fracture is now reduced, and in this manipulation it should be kept in mind that adduction, accompanied by lateral pressure applied to the inner aspect of the thigh, is helpful in unlocking the fragments. When the fracture is in alignment, the position is most easily retained by internal rotation, extension and abduction of the hip. The nail is now driven in through the lateral surface of the trochanter, at a point between the insertion of the gluteus medius and minimus and the origin of the vastus lateralis; these muscle attachments having previously been reflected subperiosteally.

As the nail enters the proximal fragment there is a tendency to separation of the fragments (fig. 6). This tendency is overcome by the use of a most valuable tool, "the impactor," which fits over the head of the nail so that the force of the blows is transmitted directly to the cortex of the femur in the subtrochanteric region, thus approximating the fragments. By alternately striking the nail and using the impactor, the nail is driven home. Impaction of the fragments is extremely important, and the nail should not be struck after impaction has been brought about, since by so doing we tend immediately to distract the fragments (fig. 7).

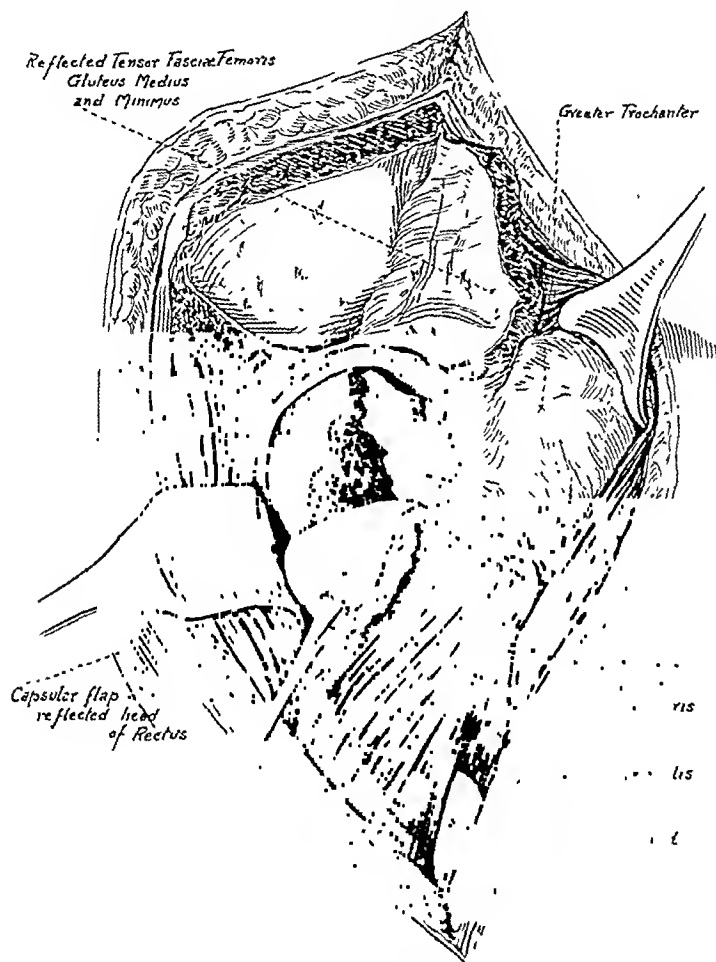


Fig. 5.—Exposure of the anterior aspect of the hip from the cotyloid ligament to the base of the trochanter.

Before closing the capsule the success of the procedure should be put to the test by moving the hip through a wide range in flexion, abduction, adduction and rotation. There is no change in the fracture line as these manipulations are carried out, and it gives the surgeon confidence in the absolute fixation so that he will start function early.

The capsular flap is now sutured back in position. Since it carries with it a portion of the reflected head of the rectus it is a strong structure and repair is

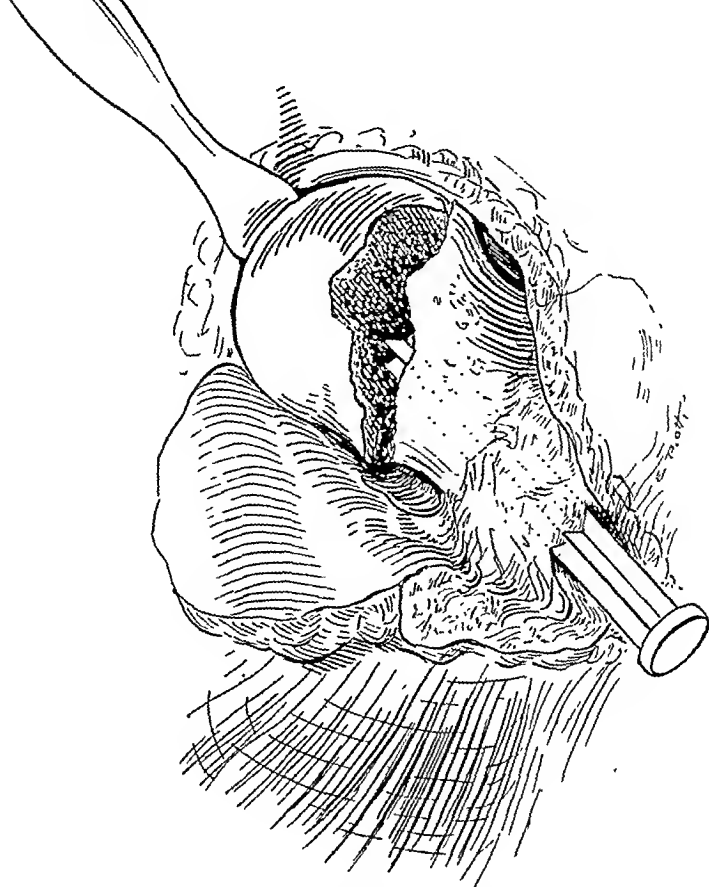


Fig. 6.—Diagram showing distraction of fracture surface as the nail enters the proximal fragments.

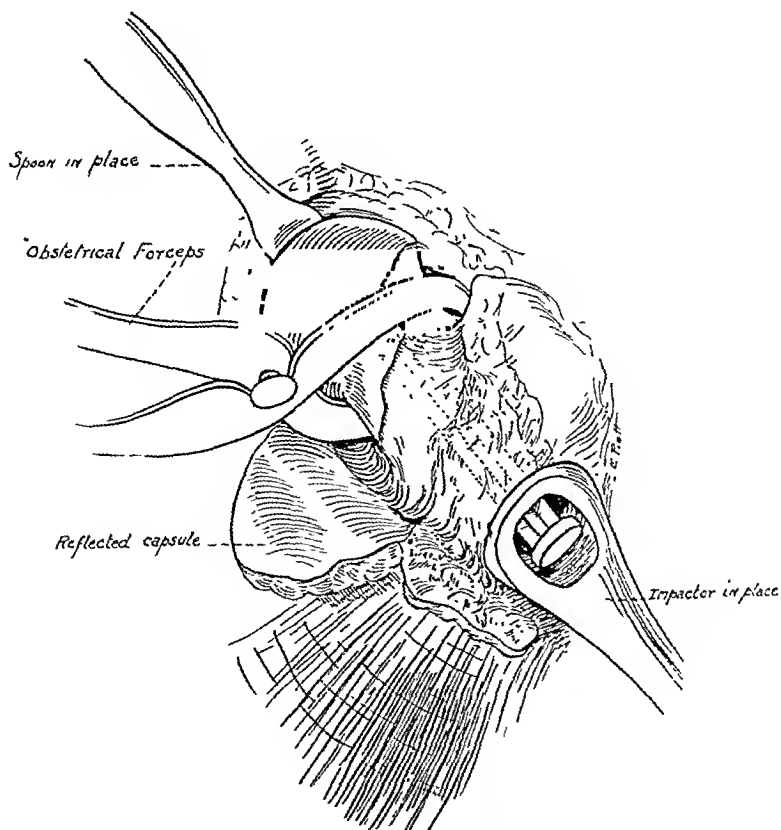


Fig. 7.—Diagram showing method of impacting the fracture.

satisfactory indeed. The muscular flap from the lateral aspect of the ilium is best sutured back into position with the hip in abduction, thereby relaxing the muscles contained in the flap. The same is true of the repair of the insertion of the tensor fascia femoris muscle. The remaining closure of the wound needs no detailed description.

ARMAMENTARIUM

In developing the technic of this procedure certain tools have been found of distinct help.

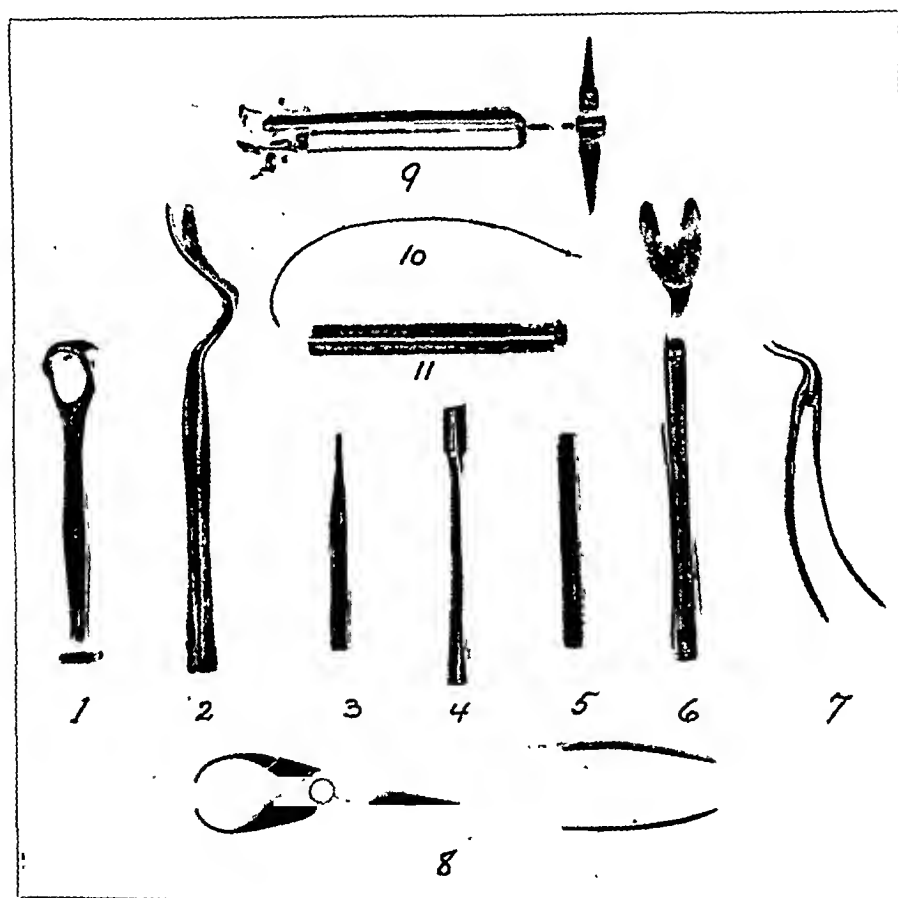


Fig. 8.—Tools used for operative technic.

The impactor (fig. 8, 1) has already been mentioned under operative technic and its use explained. Since it has been found that impaction is of great importance for the success of the operation, the impactor is indispensable.

A spatula (fig. 8, 6) is used to insert between the head of the femur and the acetabulum. It is notched so that it will fit over the ligamentum teres. The head of the femur is partially delivered from the acetabulum by means of this tool. In cases in which the head of the femur is delivered completely from the acetabulum, either to be grafted on the distal portion of the neck or to be discarded, a similar spatula with a cutting notch is used for division of the ligamentum teres (fig. 8, 2).

Nail-sets (fig. 8, 3 and 5) fit the head of the nail and are used when the nail has entered the femur to such an extent that it is no longer possible to strike it without traumatizing the soft parts.

The cortex of the femur at the base of the trochanter is extremely thick and resists the entrance of the nail to such an extent that the blades of the nail in two cases actually became bent. In order to overcome this difficulty, a starter was devised (fig. 8, 4). This is just an abbreviated nail on a handle. One of the blades of this starter projects beyond the other two which allows it to enter the cortex of the femur easily.

A distractor (fig. 8, 7) is used to facilitate the introduction of the spatula. It is inserted between the head of the femur and the acetabulum. It separates the joint surfaces so as to allow the spatula to be introduced without trauma.

An "obstetrical forceps" (fig. 8, 8) is used to grasp the neck after the fracture has been reduced. Its two blades are introduced separately, intracapsularly, and then locked. It is a distinct aid in holding the fragments in apposition and is also a guide to the superior and inferior margins of the neck.

In some instances the aiming of the nail has been faulty and the nail has had to be withdrawn so that its course might be altered. Since the cortex of the femur grasps the nail very tightly, no ordinary tool allows the withdrawal of the nail without considerable trauma. In order to facilitate this procedure, an instrument, built on the principle of the old fashioned corkscrew, is used (fig. 8, 9).

A flexible steel measure with a slide (fig. 8, 10) is used for measuring the distance from the femoral joint surface to the base of the trochanter in order to select a nail of the right length.

The nail (fig. 8, 11) as now used is made of rustless steel and has three flanges. Previously nickel steel was tried, but was found to be too soft. The flanges are $\frac{7}{32}$ inch in thickness throughout, from $\frac{1}{16}$ to $\frac{1}{4}$ inch in width, and make an angle of 120 degrees with one another. The length of the nail varies from $2\frac{1}{2}$ to 4 inches.

POSTOPERATIVE TREATMENT

In the early cases plaster casts were applied postoperatively, and these were followed by ring calipers when the patient became ambulatory. As confidence in this procedure increased, postoperative fixation was diminished and we now suspend the affected extremity and apply 5 pounds of traction. This allows the patient to move around in bed and begin function earlier. Exercises are prescribed at first for the knee and foot and, at the end of two weeks, also for the hip. At the end of three weeks a bivalved short plaster spica is made in 10 to 15 degrees of abduction. This spica is used for walking only. Because of the abducted position, weight-bearing can safely be undertaken, since in this position there is no tendency to distract the fragments. Weight-bearing is not always possible at the end of three weeks; it depends

entirely on the condition of the patient. There have been patients who have started before this time and there have also been some who have not started weight-bearing until from four to five weeks postoperatively. In cases in which expense plays no part, a jointed leather spica is used in place of the plaster. Support in the form of a plaster or leather spica should be used for a period of from three to six months, depending on the rate of repair as shown by the roentgenograms.

Removal of the nail has been undertaken at various times, varying from six months to four years. This is a very minor procedure and does not disable the patient. When the roentgenograms show bony union, the nail has ceased to function and consequently there is no objection to its removal.



Fig. 9 (case 1).—Roentgenograms taken five days before operation and two and eight months after operation.

POSTOPERATIVE COURSE

In the series of cases reported in this paper immediate postoperative reaction was slight indeed. At no time was there any need of resorting to shock measures. The outstanding reason for the absence of shock, we feel, is the nontraumatic approach. It follows structural planes, and the exposure is so satisfactory that the work on the hip joint itself can be performed without the traumatic retraction necessary in less extensive exposures. The absence of pain was very striking; as a rule, the patients are comfortable on the day of the operation.

REPORT OF CASES

CASE 1.—A. D., a youth, aged 17, a weaver, was admitted to the hospital on July 26, 1925, and discharged on October 15. He had fallen on his hip, immediate

disability resulting. A diagnosis of fracture of the distal part of the neck of the right femur was made. The fracture was of five days' duration.

The preoperative treatment consisted of traction in a Thomas splint. On August 1, under nitrous oxide anesthesia, two incisions were made: (1) a supra-articular, subperiosteal approach for exposure of the hip and (2) a short, straight incision over the trochanter for insertion of the nail. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 90. Pain was negligible. A single long spica was used for five weeks after operation, calipers with weight-bearing for seven weeks and after five and one-half months no protection was needed. The patient remained in the hospital for eighty-two days and returned to preoperative activities six months after injury.

In December, 1925, the range of motion in the operated hip was the same in every direction as that of the unoperated hip. The patient volunteered that he would not know which hip was fractured were it not for the scar.

On Jan. 19, 1926, five and one-half months after operation, the nail, which was firm, was extracted with difficulty. Roentgen examination showed that the nail apparently did not enter the head. This might have been due to distortion in the roentgenogram or it might have been actually true. At the time of operation, after the nail had been driven in, the hip could be moved through a wide range of motion without any change in the fracture. If the nail did not enter the proximal fragment, there must have been sufficient impaction to hold the fragments together.

Comment.—The excellent result in this case was due to the anatomic reduction and impaction and not to the nail. It must be remembered that this fracture was of the distal portion of the neck of the femur in a young boy, consequently an excellent result should have been obtained by any method of treatment. The roentgenograms showed bony union.

CASE 2.—J. G., a man, aged 57, a laborer in a tannery, was admitted to the hospital on Aug. 12, 1925, and discharged on September 25. He was injured by falling downstairs. A diagnosis of fracture of the middle portion of the neck of the left femur was made. The fracture was of six weeks' duration.

Prior to operation, the patient was ambulatory, crutches being used without weight-bearing. On August 18, under ethylene anesthesia, two incisions were made as in case 1: (1) a supra-articular, subperiosteal approach for exposure of the hip and (2) a short, straight incision over the trochanter for insertion of the nail. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. Pain was negligible. Following operation, suspension in a Thomas splint with five pounds of traction was done for nine days. A short plaster spica was used for six weeks, then weight-bearing without crutches or cast. The period of hospitalization was fifteen days. The patient returned to preoperative activities three and one-half months after operation.

In September, 1929, examination showed that the patient walked with a slight limp and slight toeing out; he could sit fairly well back in a chair and cross his knees with difficulty. The left trochanter was three-eighths inch higher than the right. The scar was elastic and not sensitive. Active and passive motions were as follows: external rotation, from 5 to 10 degrees; internal rotation, none; permanent



Fig. 10 (case 2).—Roentgenograms taken on Aug. 10 and 19, 1925, and four years after operation. The photographs show the functional results four and a half years after operation.

flexion, from 20 to 25 degrees; motion in flexion, 75 degrees; abduction, 5 degrees, and adduction, 10 degrees. In the knee there was no permanent flexion, and motion in flexion was normal.

Comment.—Three and one-half months after operation, the patient was working as a laborer and walked without a limp. There was a feeling of stiffness, but no pain in the hip. Four years later he was following the same occupation, but during this time there had been increasing stiffness and some pain in both hips. Roentgenograms showed bony union and also hypertrophic changes sufficient to account for the increasing limitation of motion.

CASE 3.—A. C., a woman, aged 60, whose occupation was housework, was admitted to the hospital on Feb. 3, 1926, and discharged on June 13; she was readmitted on Jan. 12, 1927, and discharged on March 17. She was injured by a fall on a level surface. A diagnosis of fracture of the middle part of the neck of the right femur was made. The fracture was of three weeks' duration. The patient suffered from alcoholic psychosis and delirium tremens.

Before operation, treatment was given for the delirium tremens. On February 26, six weeks after injury, two incisions were made under ethylene anesthesia. There was no shock requiring treatment. The maximum temperature was 101 F., and the maximum pulse rate, 120. Pain was negligible. A plaster spica was used for two weeks after operation. The patient remained in bed for eight weeks, and on the seventy-third day after operation the Thomas caliper walking splint with weight-bearing was used. The period of hospitalization was one hundred and six days.

The patient returned to the hospital on Jan. 12, 1927, for removal of the nail. Roentgenograms showed nonunion and absorption of the neck. The nail was removed on January 22, and Whitman's reconstruction was done.

In June, 1928, examination showed that the patient walked with a limp, held the hip in external rotation and was able to sit perfectly square on a chair. There was complete extension, with flexion to 90 degrees, and the total range of abduction and adduction was from 30 to 35 degrees. There was permanent external rotation from 5 to 10 degrees, and motion in external rotation to 25 degrees. Shortening of one-half inch was noted. The knee motions were normal.

Comment.—Delirium tremens complicated the preoperative condition. There was absorption of the neck of the femur, and Whitman's reconstruction was done.

This was one of the first cases and quite instructive. Two incisions were used, which in itself was a handicap, operation was prolonged and exposure of the fracture and aiming of the nail was more difficult. Impaction had not been found to be of great importance, and too short a nail was used, giving insufficient grip on the head. Furthermore, the postoperative treatment was prolonged; the patient did not walk until ten weeks after operation. This was unquestionably a mistake. Early weight-bearing in abduction would have tended to increase nutrition, aid impaction and possibly brought about union. It is interesting that even though the first open operation failed, the secondary procedure, a Whitman reconstruction, succeeded and an excellent result was obtained.



Fig. 11 (case 3).—Roentgenograms taken on Feb. 3, March 31 and Nov. 19, 1926, on June 24, 1927, and twenty-seven months after operation. The photographs show the functional results four years after operation.

CASE 4.—V. C., a man, aged 33, a smelter, was admitted to the hospital on Sept. 13, 1926, and discharged on October 8. He was injured when hit by a truck. A diagnosis of old, ununited fracture of the middle part of the neck of the left femur was made. The fracture was of nine and one-half months' duration. Before entering the Massachusetts General Hospital, the patient was in bed without apparatus for two weeks, and walked with crutches and a cane for four and one-half months. His general condition was good.

On September 15, under ethylene and ether anesthesia, two incisions were made. There was no shock requiring treatment. The maximum temperature was 101 F., and the maximum pulse rate, 130. Pain was negligible. Bender bandage spica was used for three weeks, then the patient walked with a Thomas caliper. Weight-bearing with crutches was allowed after five weeks. The period of hospitalization was twenty-five days. The patient returned to preoperative activities five and one-half months after operation.

On September 12, the nail was easily withdrawn. It was removed because there was evidence of bursa formation around its head with pain and tenderness, and increasing limitation of motion. Since extraction of the nail, the patient has been free from symptoms and able to carry on his work as a smelter.

In September, 1929, examination showed that the patient walked with a very slight limp and sat well back in his chair without discomfort. He could cross his knees with difficulty. The passive motions were as follows: internal rotation, from 10 to 15 degrees; external rotation, from 5 to 10 degrees; abduction, from 25 to 30 degrees; adduction, 20 degrees; flexion, 80 degrees and hyperextension, 20 degrees. The active motions were: internal rotation, 10 degrees; external rotation, from 5 to 10 degrees; abduction, from 25 to 30 degrees; adduction, 20 degrees; flexion, 75 degrees; hyperextension, from 15 to 20 degrees. In the knee there was complete extension and motion in flexion to 140 degrees. Shortening of three-quarters inch was noted.

Comment.—This patient was the first to be operated on because of nonunion. The fracture was of long standing, nine and one-half months, and there had been considerable absorption of the neck. The patient's age, 33, was definitely in his favor. A very satisfactory result was obtained, enabling the patient to go back to heavy manual labor. Roentgenograms taken at the end of one year showed bony union but deformity of the femoral head and neck due to preoperative absorption.

CASE 5.—M. M., a woman, aged 54, a housewife, was admitted to the hospital on Dec. 24, 1926, and discharged on Feb. 26, 1927. She was injured by a fall on a level surface. A diagnosis of fracture of the middle part of the neck of the right femur was made. The fracture was of thirteen days' duration.

A Whitman spica was used for twelve days before operation. On Jan. 6, 1927, under ethylene anesthesia, two incisions were made. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 110. Pain was negligible. Suspension in a Hodgen splint was done for five weeks after operation, then a short plaster spica in abduction. The patient was walking with crutches and a spica six weeks after operation. The period of hospitalization was sixty-three days. On September 22, the nail, which was somewhat loose and corroded, was removed.

In September, 1929, examination showed that the patient walked without a limp and no toeing out; she could sit normally, there was no lordosis and she could cross her knees while sitting. The trochanters were of the same level, and there was no scar sensitiveness. The passive motions were as follows: flexion, thigh to abdomen; abduction, 30 degrees; adduction, 20 degrees; internal rotation,

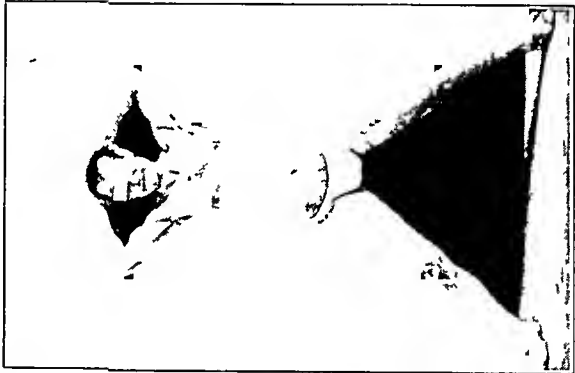


Fig. 12 (case 4).—Roentgenograms taken on Aug. 17 and Sept. 27, 1926, on Oct. 9, 1927, and three years after operation. The photographs show the functional results four years after operation.

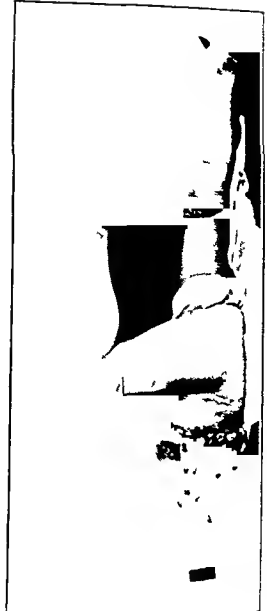
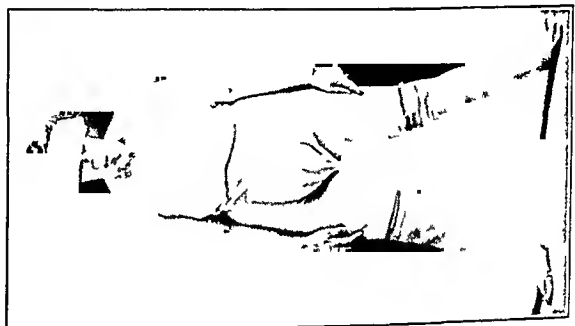


Fig 13 (case 5) —Roentgenograms taken on Dec 24, 1926, May 10, 1927, Sept 13, 1927, and sixteen months after operation. The photographs show the functional results three years after operation.

15 degrees; external rotation, 35 degrees; hyperextension, from 10 to 15 degrees. The active motions were the same as the passive. There was no shortening nor atrophy.

Comment.—A splendid result was obtained. It was difficult to detect any difference in the function of the two hips. Roentgenograms showed bony union five months postoperatively.

CASE 6.—M. D., a woman, aged 48, a housewife, was admitted to the hospital on March 4, 1926, and was discharged on July 10. She was injured by a fall on the ice. A diagnosis of fracture of the middle part of the neck of the left femur was made.

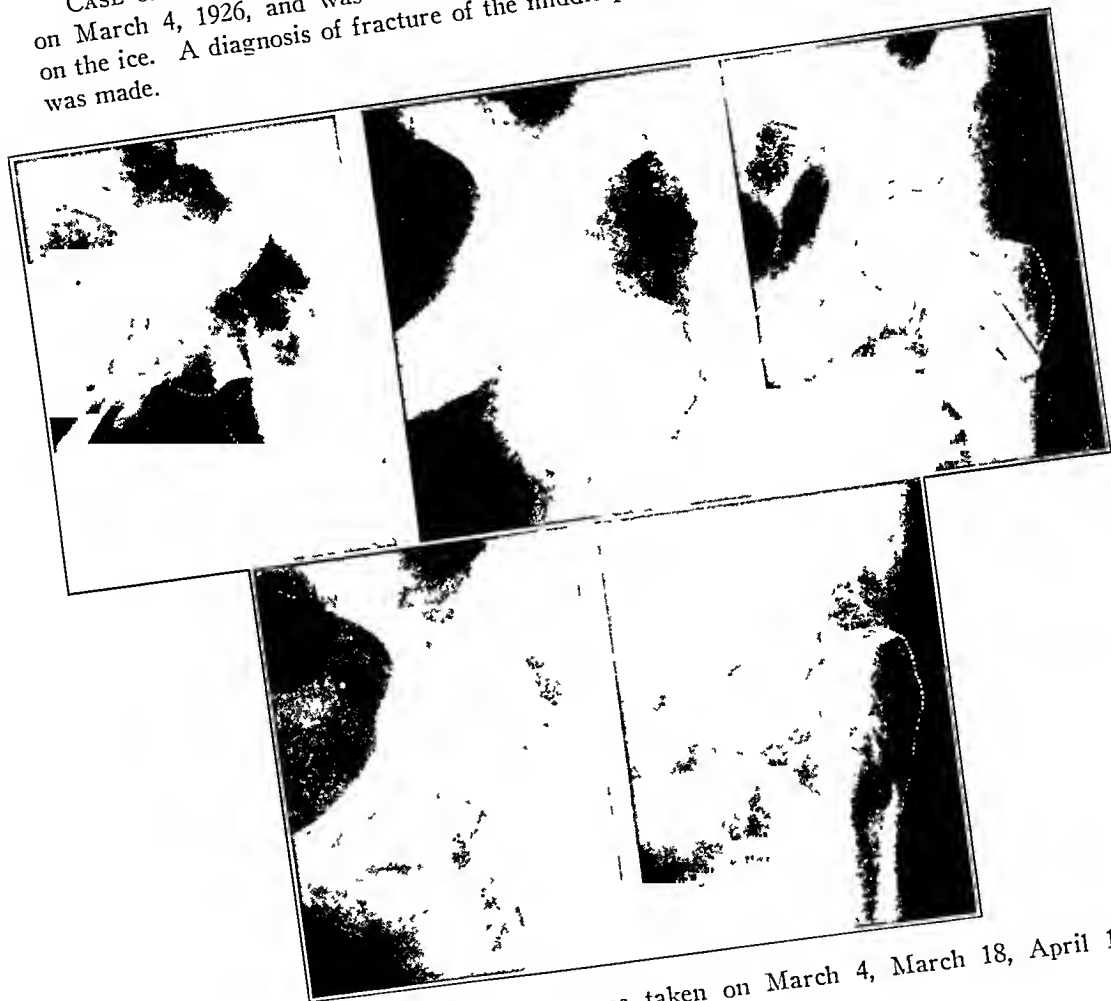


Fig. 14 (case 6).—Roentgenograms taken on March 4, March 18, April 19 and May 17, 1926, and on May 3, 1928.

Prior to operation the patient was placed in a recumbent position and sandbags applied. On March 17, two incisions were made. There was no shock requiring treatment. After operation the patient remained in bed with a Bender bandage spica for seven weeks, and at two months postoperatively she walked with crutches. Weight-bearing with crutches was done five months postoperatively. The period of hospitalization was one hundred and fifty days. Because the patient complained of pain in the hip and because of the close proximity of the nail to the joint, the nail was removed in June, 1926. She continued to walk with crutches because of pain in the hip, and roentgenograms showed nonunion. She was readmitted to the hospital on Jan. 30, 1930, and a Whitman reconstruction was performed.

Comment.—Again a failure occurred that must be attributed to lack of knowledge. Impaction was not sufficient. Early function in the abducted position was not emphasized. On the evidence of a distorted roentgenogram, it was thought that the nail came too close to the joint surface and consequently it was extracted too early.

CASE 7.—E. R., a woman, aged 67, a dressmaker, was admitted to the hospital on March 1, 1927, and discharged on May 5. She was injured by a fall on a level surface. A diagnosis of fracture of the middle part of the neck of the right femur was made. The fracture was of twelve days' duration. Opinions as to advisability of operation differed because of the patient's poor physical condition.

Before operation, suspension in a Thomas splint with 10 pounds of traction was done. On March 12, two incisions were made under ethylene anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F, and the maximum pulse rate, 90. Very little pain was felt. Suspension with light



Fig. 15 (case 7).—Roentgenograms made before operation and two months and one year after operation.

traction was done for four weeks after operation, then weight-bearing with a short plaster spica and crutches. The patient was discharged walking with crutches.

Roentgenograms in May, 1928, showed bony union at the site of the fracture. Examination in March, 1929, showed that the patient walked well without any support and with only a slight limp. There was no permanent flexion. There was motion in flexion to 100 degrees; abduction, 15 degrees, adduction, 10 degrees; internal rotation, 10 degrees and external rotation, 15 degrees. The patient died in November, 1929, from malignant disease, probably cancer of the stomach.

Comment.—The patient was in poor physical condition, so much so that advisability of operation was questioned. No shock occurred from operation, but because of general weakness the patient was slow to learn to walk. The post-operative course was marked by absence of pain. Roentgenograms taken a year after operation showed bony union.

CASE 8.—A. T., a woman, aged 56, a laundress, was admitted to the hospital on March 23, 1927, and discharged on June 21; she was readmitted on Nov. 18, 1927, and discharged on April 11, 1928. Injury resulted from a fall on a level surface. A diagnosis of fracture of the middle third of the neck of the left femur was made. The fracture was of ten days' duration.

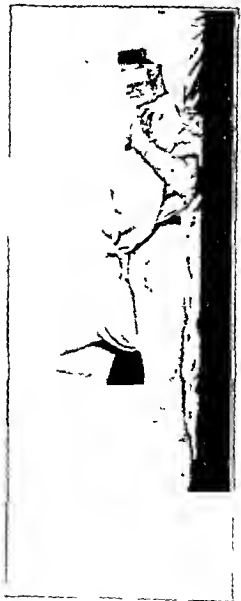
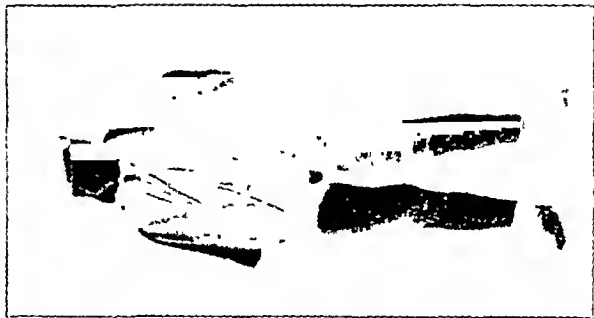


Fig. 16 (case 8).—Roentgenograms taken on March 23, 1927, one month after operation, on Nov. 8, 1927, and two months after the Whitman reconstruction. The photographs show the functional results three years after operation.

Preoperative treatment consisted of traction in a Thomas splint. On April 2, two incisions were made under ether anesthesia. The patient was in a state of moderate shock, but required no special treatment. The maximum temperature was 101 F., and the maximum pulse rate, 90. Suspension in a Hodgen splint was uncomfortable so sandbags were substituted. One month postoperatively, phlebitis of the left leg developed. The patient walked with crutches two months postoperatively, but did not bear much weight on the injured leg.

She was readmitted to the hospital on Nov. 18, 1927. She had been staying in a nursing home where she walked with crutches but did little weight-bearing. For the three weeks previous to readmission she had not been able to bear any weight on the injured leg. Roentgenograms showed nonunion. On November 25, the nail was removed, and Whitman's reconstruction performed.

Comment.—The first operation failed, probably because of insufficient impaction. The patient was only 56 years old, so the failure cannot be accounted for on the



Fig. 17 (case 9).—Roentgenograms taken on April 29 and June 14, 1927, and two months after operation.

basis of age. At the time of operation the direction of the nail had to be altered. This additional trauma may have interfered with circulation sufficiently to account for the nonunion. Other cases in which this had to be done have gone on to union, however. This patient obtained a good result from the reconstruction of the hip and is now walking with a cane.

CASE 9.—L. C., a woman, aged 80, with no occupation, was admitted to the hospital on April 29, 1927, and died on August 19. She was injured by a fall on a level surface. A diagnosis of fracture of the subcapital portion of the neck of the right femur was made. The fracture was of a few hours' duration. The patient's general condition was poor.

The preoperative treatment consisted of suspension in a Thomas splint. On May 4, one incision was made under ethylene anesthesia. There was no shock requiring treatment. The maximum temperature was 103 F., and the maximum pulse rate, 118. There was a moderate amount of pain. The patient was started

on exercises between three to four weeks after operation. She began to walk with a split plaster spica from seven to eight weeks postoperatively. Three weeks after operation there was a superficial stitch abscess which increased until a sinus was established down to the joint. The wound sepsis never cleared up. A positive blood culture, *Staphylococcus aureus*, was finally obtained, and the patient died on August 19, one hundred and five days after operation. Autopsy showed pyarthrosis, with nonunion, and nephritis.

Comment.—This patient is the oldest in the series. She stood the operation well, and the immediate postoperative course was very satisfactory. Her temperature was normal from the third day after operation until the twenty-first day. At this time a superficial stitch abscess developed. This extended and resulted in the condition which was the direct cause of the fatal outcome. This was the first case in which one incision was used; consequently the operative technic was simplified, and even though the patient was 80 years old there was no postoperative shock requiring treatment. The importance of impaction even at this time was not sufficiently recognized. Roentgenograms taken at the end of two months showed no evidence of bony union, but no change in relationship of the bony fragments.

CASE 10.—W. W., a man, aged 22, a rigger, was admitted to the hospital on April 6, 1928, and discharged on November 27. He had been thrown between two turnstiles after catching his foot in a moving rope. A diagnosis of fracture of the distal part of the neck of the left femur, fracture of the middle third of the shaft of the left femur and fracture of the capitellum of the left humerus was made. The fractures were of one and one-half hours' duration. The patient's general condition was good.

Prior to operation the fracture of the elbow was treated, and a Thomas splint with traction was used for the left hip. On April 9, one incision was made under gas oxygen and ether anesthesia. There was no shock requiring treatment. The maximum temperature was 101 F., and the maximum pulse rate, 130. Pain was negligible. Suspension in a Thomas splint with skeletal traction was applied for six weeks after operation, then a plaster spica for twelve weeks. On August 23, eighteen weeks after operation, the patient refractured the femoral shaft while turning over in bed. The period of hospitalization was eight months at the first admission.

On August 31, open reduction of the fracture of the shaft of the left femur was done for nonunion. The Sherman plate and osteoperiosteal graft were used.

On Aug. 21, 1929, the nail and Sherman plate were removed. A walking caliper splint was used until June, 1929, then the patient walked with a cane.

In October, 1929, examination showed that the patient walked with a slight limp and did not toe out. He could sit well back in a chair and could cross his knees without difficulty. The trochanters were of the same level; the scars were elastic and not tender. Passive motions were as follows: internal rotation, 20 degrees; external rotation, 35 degrees; abduction, 30 degrees; flexion, complete; extension, 15 degrees hyperextension. The active motions were the same as the passive. In the knee there was permanent flexion of 5 degrees and motion in

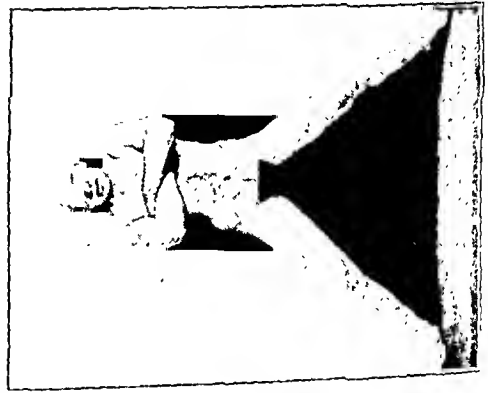
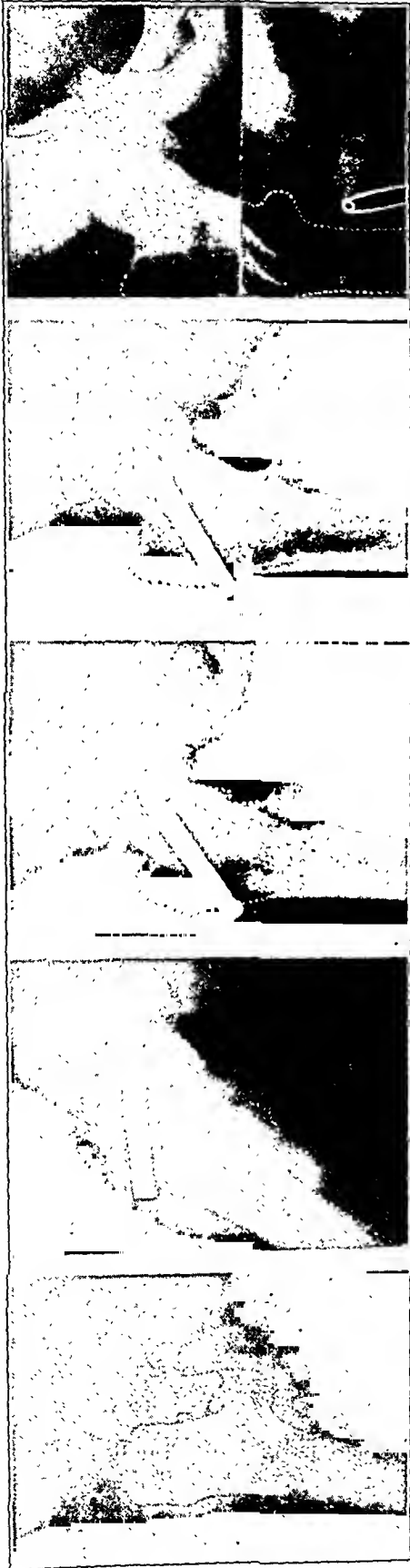


Fig. 18 (case 10).—Roentgenograms of the fracture of the neck and of the shaft taken ten weeks, six, fourteen and sixteen months after operation. The photographs show the functional results one year after operation.

flexion of 70 degrees. Shortening of $\frac{3}{4}$ inch and atrophy of the thigh of $1\frac{1}{4}$ inches were noted.

Comment—This case is interesting because of two fractures of the femur; one had to be eliminated in order to treat the other satisfactorily. The hip fracture was consequently nailed, and the shaft fracture treated by skeletal traction. Progress was satisfactory until a bivalved plaster spica was applied and exercises started. The patient then refractured the femoral shaft, and plating accompanied by osteoperiosteal graft had to be resorted to. There was a successful outcome

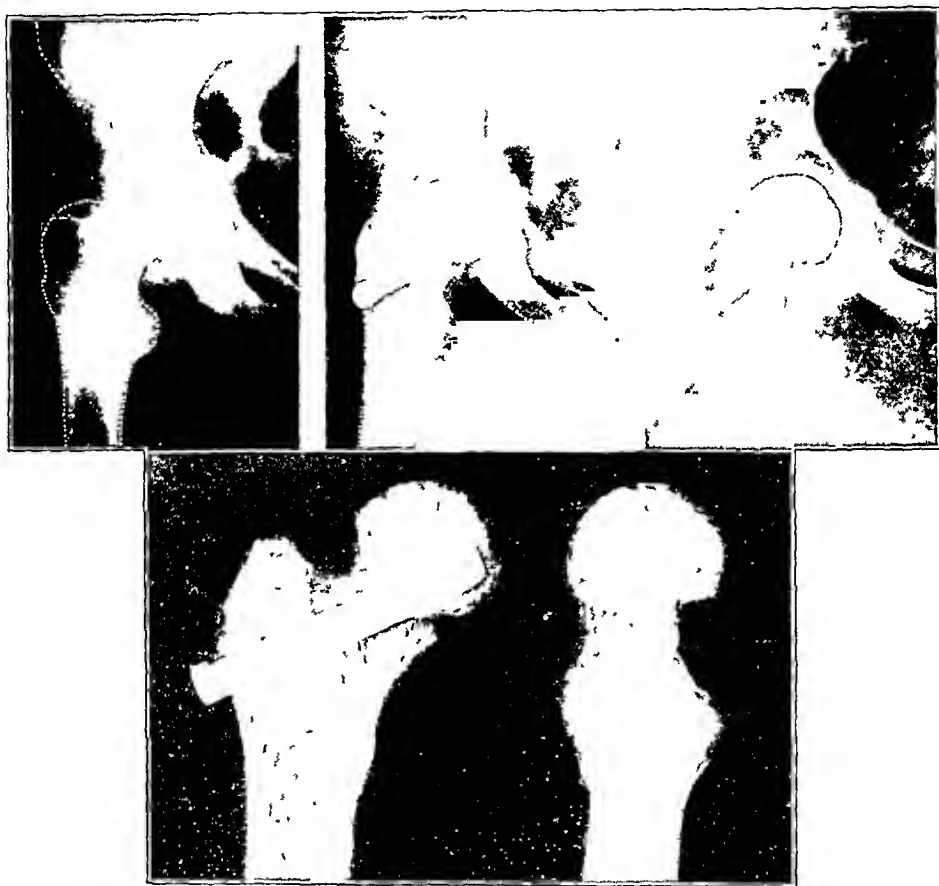


Fig. 19 (case 11).—Roentgenograms taken before operation and four and six weeks after operation.

of both fractures but limitation of knee motion because of prolonged immobilization. The nail and Sherman plate were later removed, not because of any local condition demanding it, but because of the feeling of the fracture service that hardware should be removed after it had ceased to function. Roentgenograms showed bony union at the end of six months.

CASE 11—A. N., a woman, aged 52, was admitted to the hospital on Aug. 2, 1928, and died on October 4. She was injured by a fall on a level surface. A diagnosis of fracture of the subcapital portion of the neck of the right femur was made.

Prior to operation, the patient was placed on a Bradford frame, with a pillow and side splints to the leg; later traction and a Thomas splint were used. On August 9, one incision was made under ethylene anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. Suspension and light traction were applied for sixteen days after operation, then the patient walked with crutches and a short spica; no pain was felt. The period of hospitalization was sixty-four days.

Comment.—Eight weeks after operation, the patient was walking about the ward on crutches when she suddenly collapsed and died in twenty-four hours. Autopsy demonstrated acute hemorrhagic pancreatitis as the cause of death. The hip showed excellent position of fragments and bony union, which was demonstrated microscopically and by roentgenograms of the specimen removed. This was the second case in which impaction was purposely produced at the time of operation, and this unquestionably accounted for bony union.

CASE 12.—S. M., a woman, aged 66, a housewife, was admitted to the hospital on Aug. 11, 1928, and discharged on October 30. She was injured by a fall on the level surface. A diagnosis of fracture of the distal third of the neck of the left femur was made. The fracture was of fourteen days' duration. The patient's general condition was poor because of a cardiac condition.

Preoperative treatment consisted of suspension in a Thomas splint with light traction, digitalization and rest. On August 24, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 101 F., and the maximum pulse rate, 120. Pain was very slight. Suspension in a Thomas splint with traction was applied for four weeks, then walking caliper without weight-bearing for four weeks. Weight-bearing began two months postoperatively. The patient was discharged using crutches and a toe drop splint. The toe drop, which was not accounted for, developed postoperatively. The period of hospitalization was eighty days. The patient returned to preoperative activities eleven months postoperatively, July, 1929.

In May, 1930, examination showed that the patient walked with a slight limp and slight toeing out. She sat normally and could cross her knees while sitting. The left trochanter was about one-half inch above the right; the scar was not sensitive. Passive motions were as follows: internal rotation, 5 degrees; external rotation, from 25 to 30 degrees; adduction, 15 degrees; abduction, 10 degrees; flexion, normal; hyperextension, 15 degrees. Active motions were the same. In the knee extension and flexion were complete. There was three-eighths of an inch shortening and no atrophy.

Comment.—Digitalization was done before operation. This is the first case in which spinal anesthesia was used. The postoperative toe drop cleared up in six months. The end-result was excellent. Roentgenograms showed bony union at the end of one year.

CASE 13.—C. C., a woman, aged 55, a housewife, was admitted to the hospital on Aug. 13, 1928, and discharged on October 25. She was injured by a fall down stairs. A diagnosis of fracture of the distal third of the neck of the left femur was made. The general condition of the patient, who was obese, was fair.

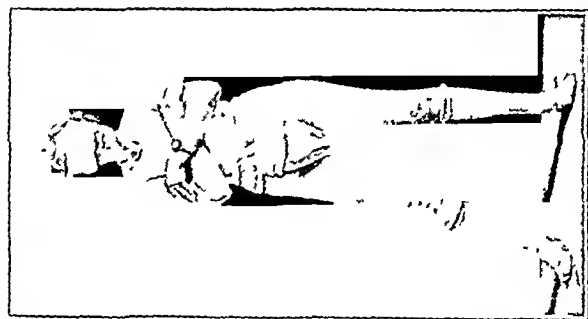
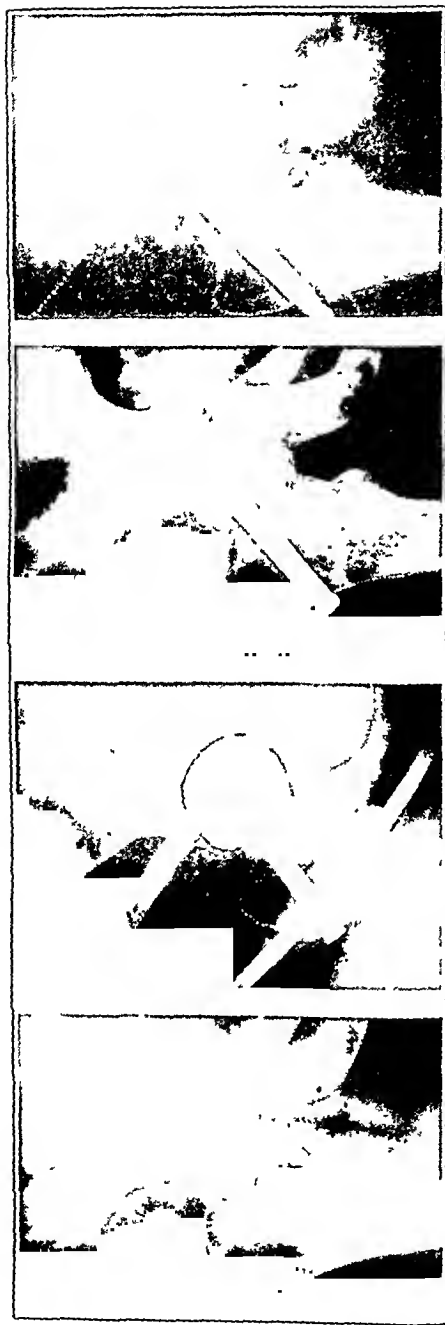


Fig. 20 (case 12).—Roentgenograms taken before operation and twelve days, seven weeks and one year after operation. The photographs show the functional results twenty-two months after operation.

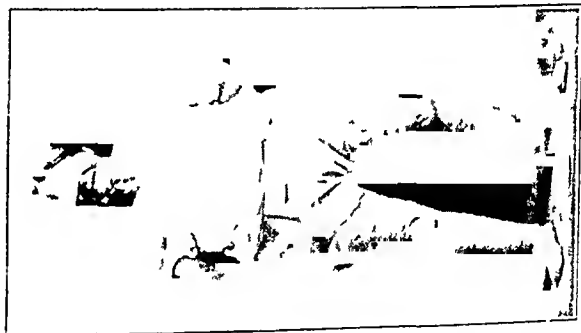
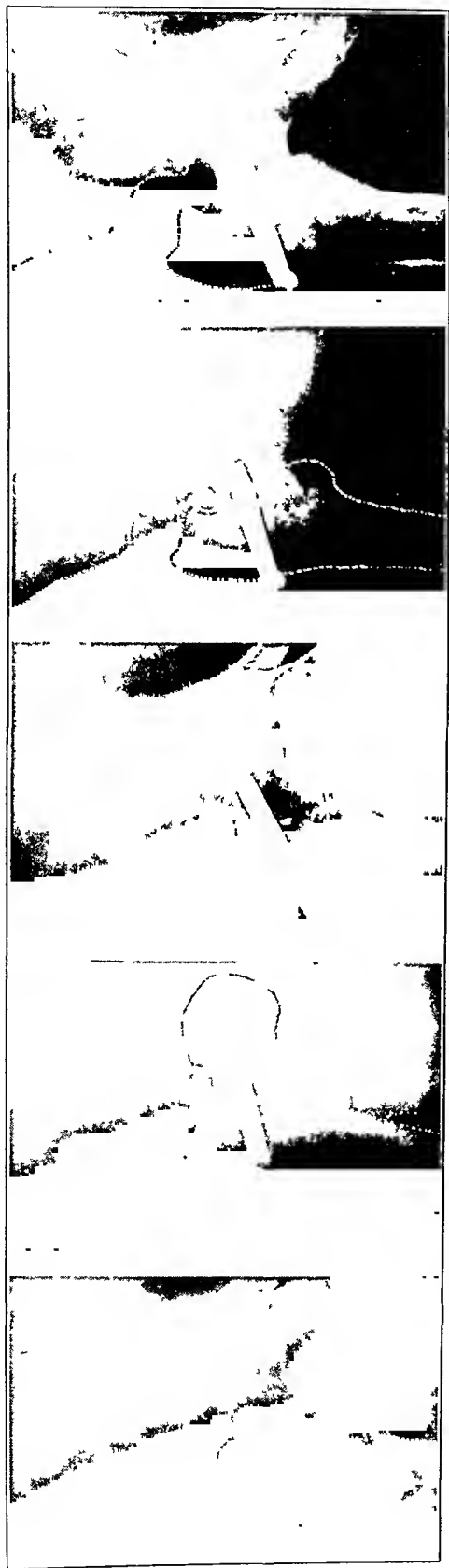


Fig. 21 (case 13).—Roentgenograms taken on Aug. 11 and 25, 1928, and two, six and thirteen months after operation. The photographs show the functional results one year after operation.

On August 24, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 95. Pain was negligible. Suspension in a Thomas splint with light traction was applied for ten days, then a short plaster spica was used. The patient was ambulatory three weeks later; weight-bearing without crutches was allowed eight weeks postoperatively. The period of hospitalization was seventy days. The patient returned to preoperative activities three months after operation.

In August, 1929, examination showed that the patient could walk without a limp or toeing out, could sit well back in a chair and could cross her knees while sitting. The left trochanter was one-quarter inch higher than the right; the scar was elastic and not sensitive. Passive motions were as follows: internal rotation, 15 degrees; external rotation, 40 degrees; abduction, 30 degrees; adduction, 15 degrees; flexion, 120 degrees; extension, complete. Active motions were the same as the passive. In the knee there was complete flexion and complete extension. There was no shortening or atrophy.

Comment.—The distal third of the neck of the left femur was fractured. Roentgenograms at the end of six months showed bony union.

CASE 14.—C. J., a woman, aged 66, a laundress, was admitted to the hospital on Sept. 2, 1928, and discharged on October 31. She was injured by a fall downstairs. A diagnosis of fracture of the middle part of the neck of the left femur was made. The duration of the fracture was eight days.

Preoperative treatment consisted of digitalization and a Thomas splint with light traction. On September 10, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 101 F., and the maximum pulse rate, 110. Pain was negligible. Suspension in a Thomas splint with light traction was applied after operation. Three weeks postoperatively, a short plaster spica was used, and weight-bearing was allowed. The period of hospitalization was fifty-six days.

In March, 1930, examination showed that the patient walked with a limp and toed out. She sat well back in a chair; there was no lordosis, but she could not cross her knees while sitting. Passive motions were as follows: internal rotation, 10 degrees; external rotation, 25 degrees; abduction, 25 degrees; adduction, 15 degrees; flexion, 90 degrees; permanent flexion, 5 degrees. Active motions were: internal rotation, from 5 to 10 degrees; external rotation, from 15 to 20 degrees; abduction, 25 degrees; adduction, from 5 to 10 degrees; flexion, 70 degrees. In the knee, extension lacked 5 degrees and there was motion in flexion to 120 degrees. Shortening of $1\frac{1}{2}$ inches and slight atrophy were noted.

Comment.—In July, 1929, nine months after discharge from the Massachusetts General Hospital, the patient fell, sustaining a subtrochanteric fracture of the same femur. She was treated at another hospital, in bed, for eleven weeks. This fracture united, but in malposition resulting in marked shortening. In spite of this, hip motions remained excellent. Roentgenograms showed bony union, although there was considerable deformity of the head and neck of the femur.

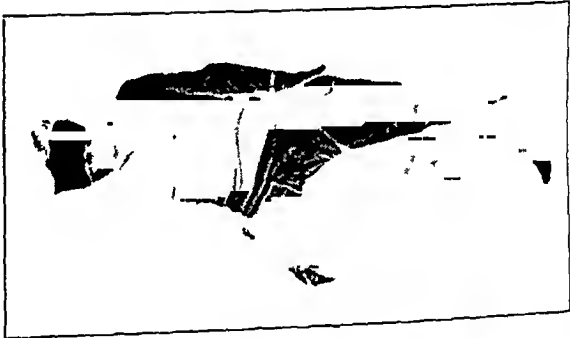
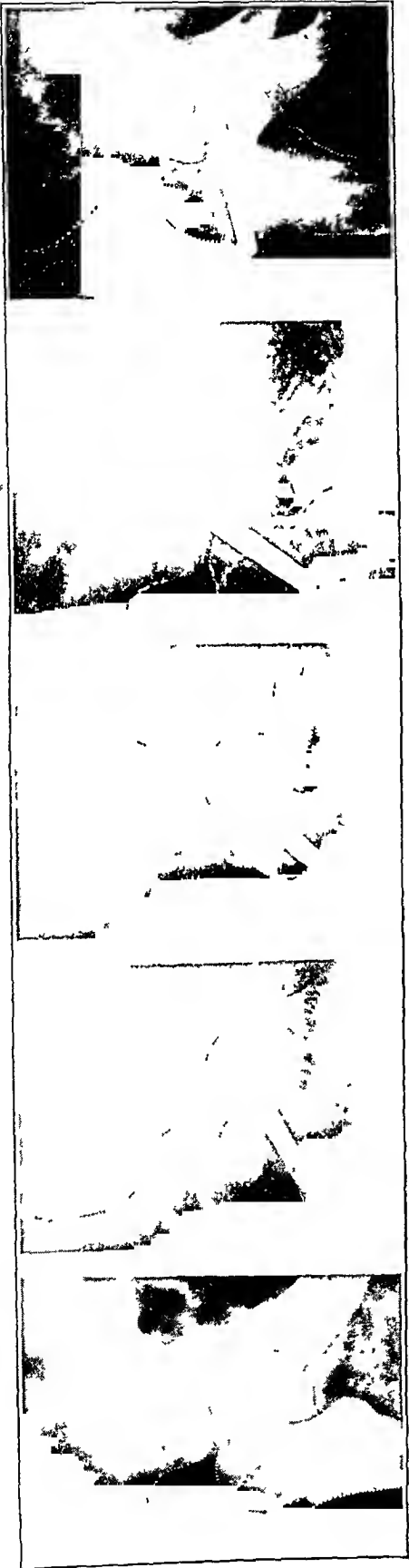


Fig. 22 (case 14) —Roentgenograms taken before operation and on Sept 2 and 11, 1928, and two and five weeks after operation. The photographs show the functional results one and one-half years after operation

CASE 15.—A. B., a woman, aged 62, a telegraph operator, was admitted to the hospital on Feb. 15, 1929, and died on March 14. She was injured by a fall on the stairs. A diagnosis of fracture of the middle part of the neck of the left femur was made. The fracture was of six days' duration.

Preoperative treatment consisted of suspension in a Thomas splint with light traction. On February 21, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 105 F., and the maximum pulse rate, 130. Pain was negligible. Postoperative treatment consisted of suspension with mild traction and a Thomas splint. The period of hospitalization was twenty-eight days.

Comment.—On the morning of the operation the patient had a temperature of 102.8 F., which was not brought to the attention of the surgeon. After operation, the temperature dropped steadily to normal on the sixth day. During this time she was listless, very much distended and refused practically all her feedings.



Fig. 23 (case 15).—Roentgenograms taken before operation and two days after operation.

On the eighth day, the temperature began to rise steadily to 105 F., where it remained until the time of her death, twenty-one days after operation. Her pulse remained between 100 and 120. There was no local evidence of infection until the fifteenth day after operation. On that day the wound began to discharge serosanguineous material; culture showed *Staphylococcus aureus*. Blood culture showed the same organism. An autopsy was not obtained. Postoperative roentgenograms showed excellent position of the nail with complete reduction of the fracture. The postoperative course suggests probable hematogenous infection.

CASE 16.—A. H., a man, aged 36, a bookbinder, was admitted to the hospital on Feb. 18, 1929, and discharged on April 13. Injury was caused by a fall on a level surface. A diagnosis of fracture of the middle part of the neck of the left femur was made. The fracture was of five weeks' duration. The patient's general condition was excellent.

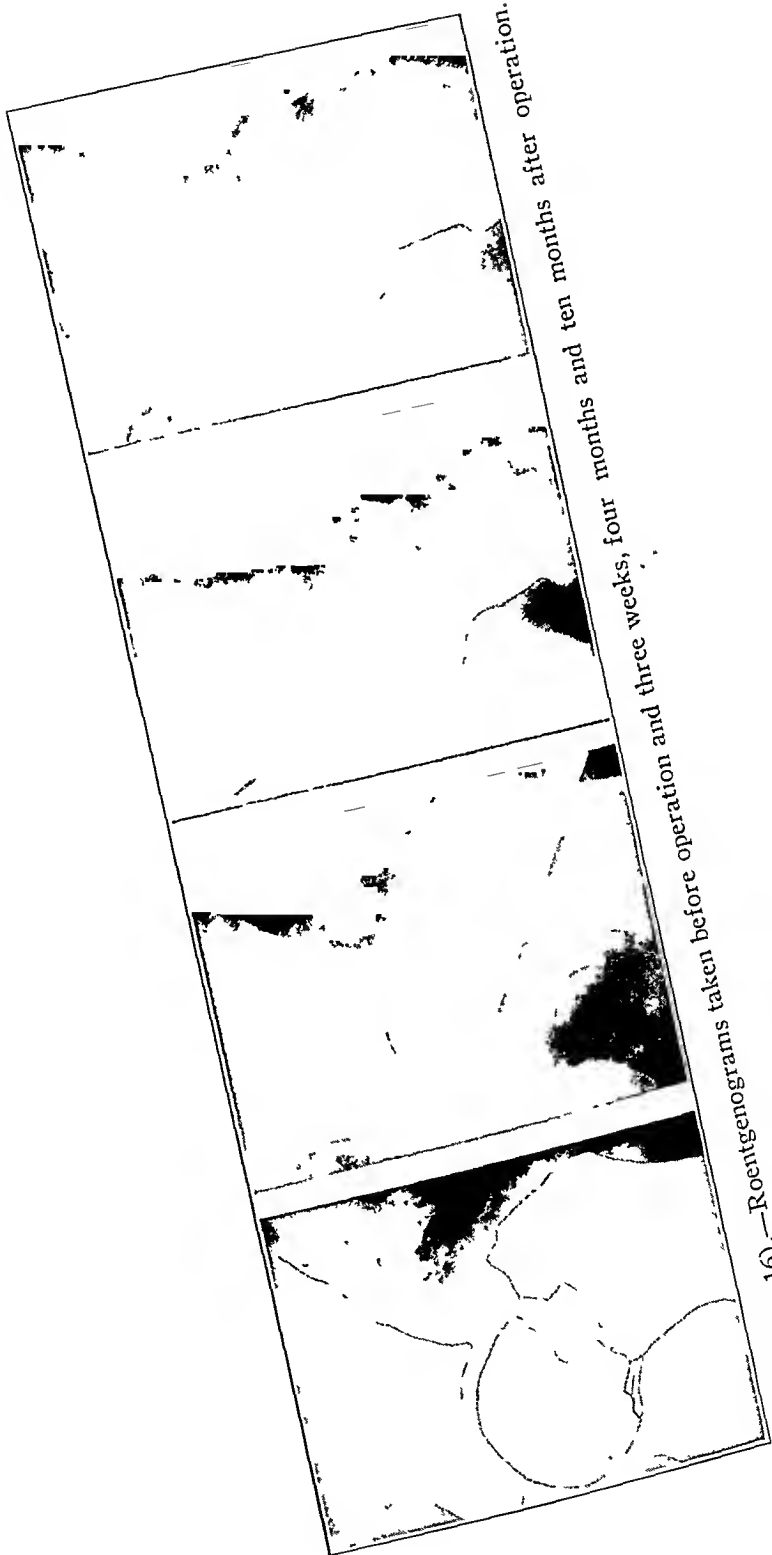


Fig. 24 (case 16).—Roentgenograms taken before operation and three weeks, four months and ten months after operation.

A Whitman spica was used for five weeks prior to operation. On March 23, one incision was made under ether anesthesia. There was no shock, and the post-operative course was entirely uneventful. Pain was negligible. Weight-bearing in a short spica was done eleven days after operation. The patient was discharged from the hospital twenty-one days after operation.

One year after operation the patient walked without a limp, and there was no shortening. Motions of the left hip were the same as on the right. Motions of the knee joint were normal.

Comment.—This patient was operated on in Oslo, Norway, consequently the notes are not as complete as in the cases personally followed after operation. The patient had excellent attention from the surgeon in charge, Dr. Wideroe, and got up on the eleventh day after operation, walking in a short spica with crutches. This is the earliest weight-bearing in any case. The result is remarkable. Results of the examination were furnished me by Dr. Wideroe who saw the patient one year after operation. The roentgenograms taken at the end of four months showed bony union.

CASE 17.—G. L., a woman aged 48, a bookkeeper, was admitted to the hospital on March 15, 1929, and discharged on June 10. She was injured by a fall on a level surface. A diagnosis of fracture of the middle third of the neck of the left femur was made. The fracture was of twenty-seven days' duration. The patient's general condition was fair, being complicated by syphilis of the central nervous system.

Preoperative treatment consisted of a Thomas splint and traction. On March 23, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 102 F., and the maximum pulse rate, 100. Pain was negligible. Suspension in a Thomas splint and light traction were used for three weeks, then weight-bearing with a short plaster spica and crutches. The period of hospitalization was ninety days.

In March, 1930, examination showed that the patient walked with a slight limp, toed out slightly, could sit normally, had no lordosis and could cross her knees while sitting. The trochanters were on the same level; there was no scar-sensitiveness. Passive motions were as follows: internal rotation, 15 degrees; external rotation, 25 degrees; abduction, 25 degrees; adduction, 15 degrees; flexion, 90 degrees, and complete extension. Active motions were: internal rotation, 10 degrees; external rotation, 20 degrees; abduction 25 degrees; adduction, 15 degrees, and flexion, 90 degrees. In the knee there was complete extension and motion in flexion to 90 degrees. There was no shortening or atrophy.

Comment.—The patient's condition was complicated by syphilis of the central nervous system. An excellent functional and anatomic result was obtained. Roentgenograms showed bony union at the end of nine months. Bony union in tabes speaks well for the method.

CASE 18.—S. B., a woman, aged 48, a housewife, was admitted to the hospital on July 15, 1929, and discharged on August 22. She was injured by a fall on a level surface. A diagnosis of old, ununited fracture of the middle portion of the neck of the left femur was made. The fracture was of nineteen months' duration.



Fig. 25 (case 17).—Roentgenograms taken before operation and four days, three, six and nine months after operation. The photographs show the functional results one year after operation.



Fig. 26 (case 18).—Roentgenograms taken before operation and one, three, seven and fifteen months after operation. The photographs show the functional results eleven months after operation.

The patient had been treated in another hospital by a Whitman plaster for two months, followed by a brace, physiotherapy and later crutches. Nonunion resulted. On July 19, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. Pain was negligible. Postoperative treatment consisted of suspension in a Thomas splint with mild traction. Exercises were started in one week, and the patient began to walk with a leather spica in four weeks. The period of hospitalization was forty-eight days.

In July, 1930, examination showed 100 degrees of flexion, complete extension and abduction of 30 degrees. As the patient lives in a distant city, examination of the end-results is not complete.

Comment.—A remarkably good functional and anatomic result was obtained in this case in spite of nineteen months' nonunion. Roentgenograms demonstrated solid bony union, and the photographs showed excellent function.

CASE 19.—E. D., a man, aged 72, with no occupation, was admitted to the hospital on June 29, 1929, and discharged on September 4. He was injured by a fall downstairs. A diagnosis of fracture of the middle part of the neck of the right femur was made. The duration of the fracture was fourteen days. The patient's general condition was fair.

Preoperative treatment consisted of suspension in a Thomas splint with traction. On July 13, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. The patient was irrational for a week postoperatively, owing, it was thought, to cerebral arteriosclerosis. After this, convalescence was uneventful. Weight-bearing was begun at the end of the third week with crutches and a short plaster spica. The period of hospitalization was sixty-seven days. The patient was discharged wearing a short spica and walking with crutches. There was flexion of 80 degrees, complete extension and very little motion in rotation.

In September, 1929, examination showed that the patient could walk with a cane without pain, that he toed out, could sit well back in a chair, but could not cross his knees while sitting. The right trochanter was one-fourth inch higher than the left. The scar was elastic, but not sensitive. Passive motions were as follows: permanent external rotation, 20 degrees; external rotation, from 20 to 25 degrees; abduction, 15 degrees; adduction, 10 degrees; flexion, 85 degrees; permanent flexion, 20 degrees. The active motions were the same as the passive. In the knee, extension was complete, and there was 70 degrees flexion. Shortening of one-half inch and slight atrophy were noted.

Comment.—A good stable hip was obtained, although there was limitation of motion due to hypertrophic changes. Absence of pain was an outstanding feature throughout the treatment. Roentgenograms showed bony union but marked hypertrophic changes.

CASE 20.—J. McA., a man, aged 66, a laborer, was admitted to the hospital on May 10, 1929, and was discharged on July 30. He was injured by a fall downstairs. Diagnosis of fracture of the middle part of the neck of the right femur was made. The duration of the fracture was twenty-one days. The general condition of the patient was fair.



Fig. 27 (case 19).—Roentgenograms taken before operation and eighteen days, six weeks, five and seven months after operation. The photographs show the functional results nine months after operation.

Preoperative treatment consisted of digitalization and suspension in a Thomas splint with light traction. On May 25, one incision was made under spinal anesthesia. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. Pain was negligible. Suspension in a Thomas splint with light traction was used for six weeks, weight-bearing with a plaster spica and crutches for two weeks, then weight-bearing with crutches alone. There was no pain in the hip, but some in the knee.



Fig. 28 (case 20).—Roentgenograms taken before operation and three days and two months after operation.



Fig. 29 (case 21).—Roentgenograms taken before operation and three days after operation.

The end-result was not obtained as the patient died on October 23 of cerebral hemorrhage.

Comment.—This patient made an uneventful convalescence and was walking well with crutches at the time of discharge from the hospital. Since he died five months after operation with no further roentgenogram, the results cannot be classified as to success or failure. Roentgenograms taken two months post-operatively showed apparent beginning bony union.

CASE 21.—S. R., a woman aged 51, an inmate of the state infirmary, was admitted to the hospital on July 14, 1929, and discharged on September 13. She

was injured by a fall on a level surface. A diagnosis of fracture of the middle portion of the neck of the left femur was made. The fracture was of twelve days' duration. The patient's general condition was poor. She had cerebral spinal syphilis and had been an inmate of the state institution for two years. There was a history of "shock" at the age of 41 involving the left side of the face and the right arm and the leg. There was still marked weakness of these members. The Wassermann tests of the spinal fluid and blood were negative at entry.

Prior to operation, suspension in a Thomas splint with light traction was used. On July 26, one incision was made under spinal anesthesia. There was no shock requiring treatment. The temperature was normal until the fifth day postoperatively, when it reached 101 F., and on the seventh day, 103 F., due to cystitis. Postoperative treatment consisted of suspension in a Thomas splint with light traction, and then weight-bearing with a short plaster spica four weeks postoperatively. The patient was discharged on September 13, after a period of hospitalization of eight weeks. At that time the hip was in full extension, with 20 degrees of flexion, 5 degrees of internal and external rotation, 15 degrees of abduction and 10 degrees of adduction. There was no shortening or pain.

Comment.—The patient was discharged to the state infirmary and was not examined again. She died on Jan. 21, 1930, a little over six months after operation. The primary cause of death was "neurosypilis." As there was no end-result study, or roentgenograms made after discharge, this case has to remain unclassified as to success or failure. Postoperative roentgenograms showed good apposition of the fragments and good position of the nail.

CASE 22.—A. C., a woman aged 54, with no occupation, was admitted to the hospital on July 18, 1929, and discharged on September 14. She was injured by a fall on a level surface. A diagnosis of old, ununited fracture of the middle portion of the neck of the left femur was made. The patient fell in December, 1927 (nineteen months before admission), fracturing the neck of the left femur. She was on traction for six weeks, then ambulatory on crutches. Her condition at the time of admission was good except for her blood pressure which was 240 systolic and 140 diastolic.

Other than general care no specific treatment was given prior to operation. On July 25, one incision was made under spinal anesthesia. A nail without a head was driven through the femoral head from within out. The trochanter was transplanted downward on the shaft of the femur. There was no shock requiring treatment. The maximum temperature was 100 F., and the maximum pulse rate, 100. Very little pain was experienced. A double plaster spica was used for four weeks, followed by a short single spica and weight-bearing with crutches. The period of hospitalization was fifty-seven days.

In November, 1929, examination showed the patient walking with crutches, with only a slight limp and no toeing out. She could sit well back in a chair; there was no lordosis, but she could not cross her knees while sitting. The scar was mobile but not sensitive. Passive motions were as follows: internal rotation, from 5 to 10 degrees; external rotation, from 15 to 20 degrees; abduction, 20 degrees; adduction, 15 degrees; flexion, 80 degrees, and hyperextension, 10 degrees.

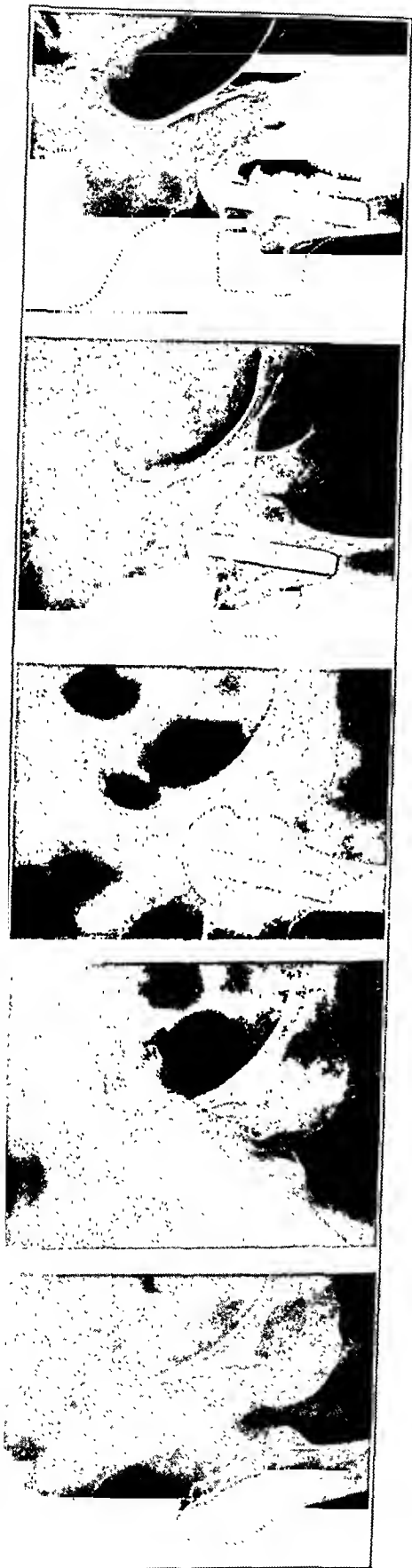


Fig. 30 (case 22).—Roentgenograms taken before operation and five days, five weeks, two and one-half and five months after operation. The photographs show the functional results four months after operation.

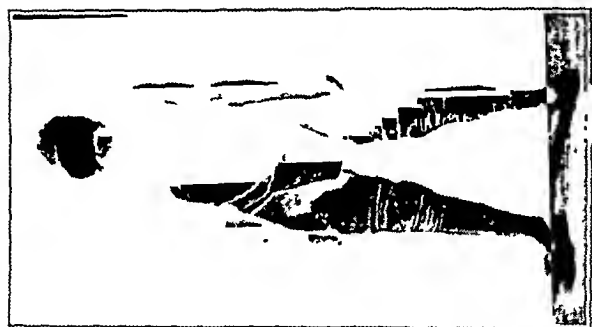
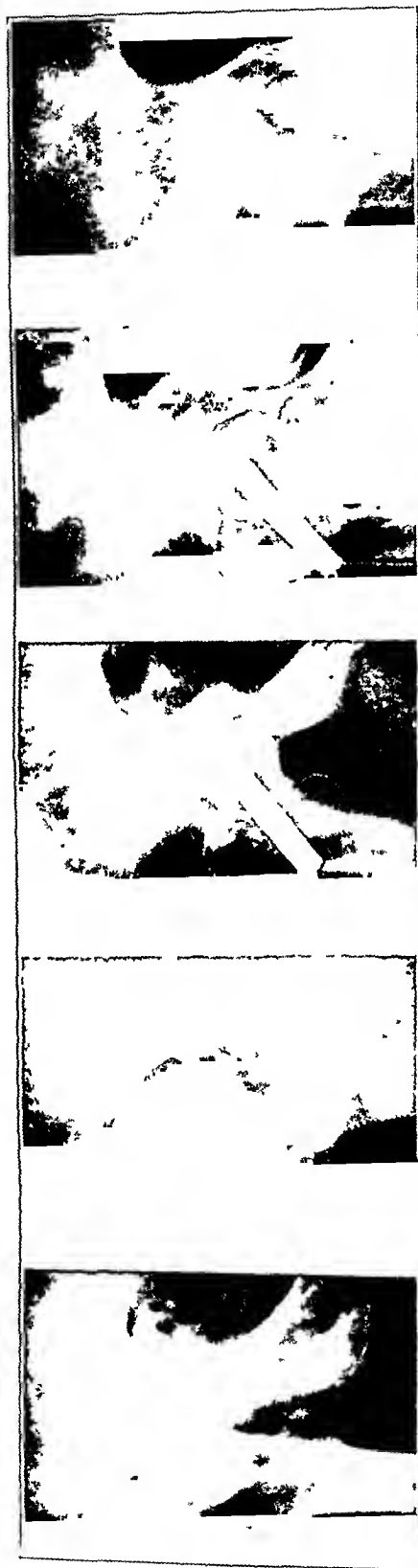


Fig. 31 (case 23).—Roentgenograms taken before operation and two days, six weeks, eleven weeks and thirteen months after operation. The photographs show the functional results seven months after operation.

Active motions were: internal rotation, 5 degrees; external rotation, 15 degrees; abduction, 20 degrees; adduction, 15 degrees; flexion, 70 degrees; hyperextension, 10 degrees. In the knee there was: complete extension and flexion to 110 degrees. There was shortening of 2 inches.

Comment.—This patient was last seen five and one-half months postoperatively, at which time she was walking with a cane and the hip showed excellent function. The roentgenograms showed no change in the relationship of the fragments, but bony union was not demonstrated. For the past ten months the patient has been confined to a psychopathic institution in a distant city, and consequently further examination has not been possible.

CASE 23.—J. C., a woman, aged 67, a housekeeper, was admitted to the hospital on Aug. 5, 1929, and discharged on November 6. She was injured when she was struck by an automobile. A diagnosis of fracture of the middle portion of the neck of the right femur was made. The head of the femur was dislocated. The fracture was of ten days' duration.

The local doctor, who was under the impression that the condition was an uncomplicated dislocation of the hip, attempted to reduce it under ether anesthesia, but was unable to do so and referred the patient to the Phillips House. On August 8, one incision was made under spinal anesthesia. The head of the femur was found dislocated and pointing anteriorly. The ligamentum teres was completely torn, and the capsule was severely lacerated. The head of the femur was removed and placed in the acetabulum, and the fracture reduced and fixed with a nail. Suspension and light traction were used for four weeks, followed by the use of a leather spica with weight-bearing. The period of hospitalization was ninety-three days.

In August, 1930, examination showed that the patient walked with a slight limp, toed out slightly and sat well back in a chair. She could not cross her knees while sitting. There were permanent flexion of 15 degrees, permanent external rotation of 5 degrees, additional external rotation of 10 degrees and motion in flexion of 10 degrees. In other words, the hip was practically stiff.

Comment.—During her convalescence the patient had a slight temperature of unknown origin until undulant fever was discovered. Since discharge from the hospital, she has been readmitted on two occasions for roentgenograms and instruction in walking. She has a stable, painless hip, but there is marked limitation of motion due to hypertrophic changes, the result of the original severe trauma. The roentgenograms showed bony union.

CASE 24.—J. P. R., a man, aged 50, a professor, was admitted to the hospital on Aug. 23, 1929, and discharged on November 12. He was injured by a fall on a marble floor. A diagnosis of old ununited fracture of the middle part of the neck of the femur of the left hip was made. The fracture was of fifteen months' duration.

The picture was complicated by an extensive poliomyelitis, weakness of the knee extensors and absence of the foot extensors on the side of the fracture. The patient was treated at another hospital on a Bradford frame with traction. The original roentgenograms showed "impacted" fracture. At the end of seven weeks, the patient was sent home, still recumbent. He began getting up in the fall of 1928, and since then has been walking with two canes. Roentgenograms taken fifteen months after injury showed nonunion.

On August 26, one incision was made under spinal anesthesia. There was quite satisfactory reduction considering the marked bone atrophy due to fifteen months disuse and poliomyelitis. There was no shock requiring treatment. The maximum

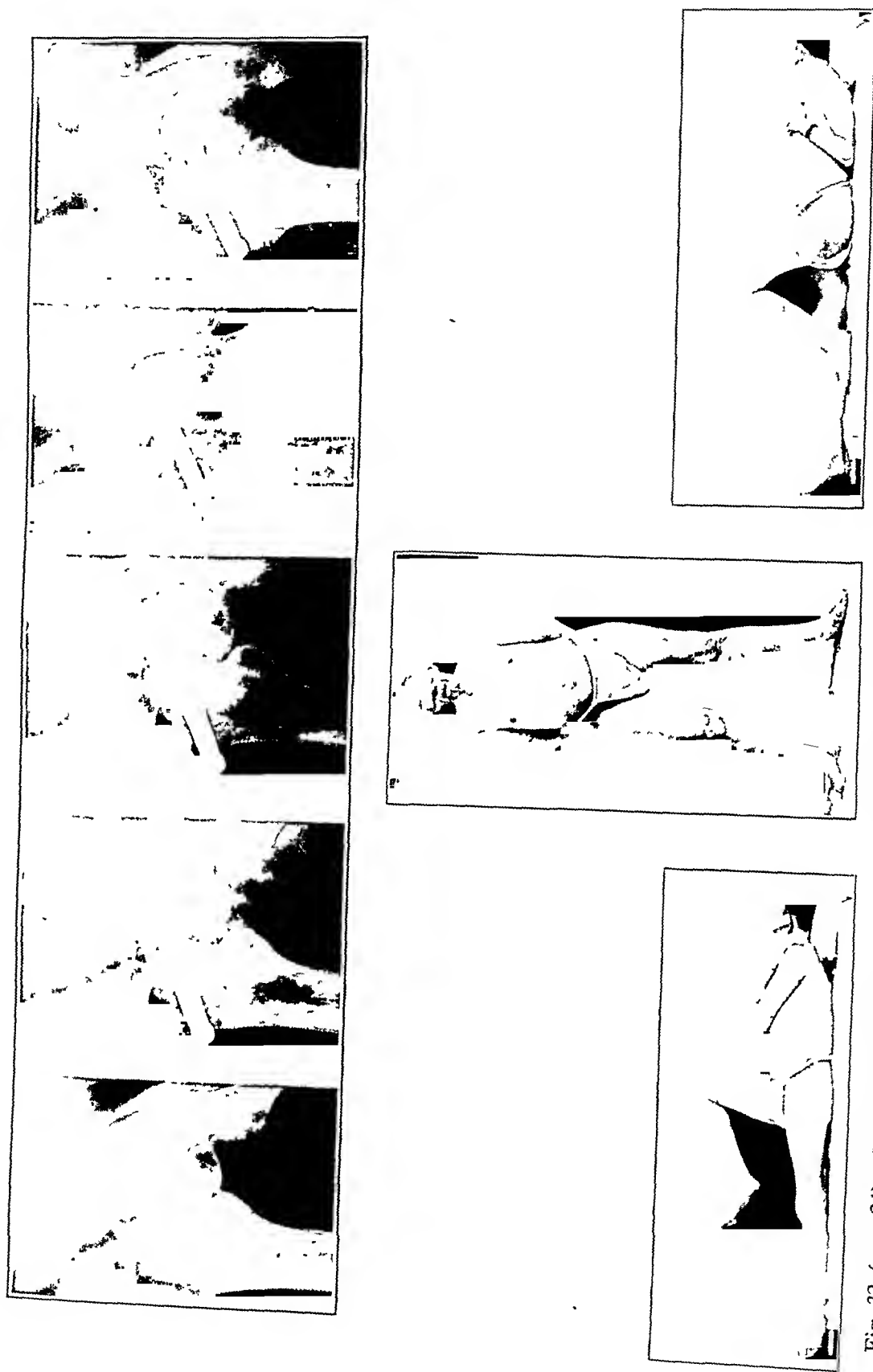


Fig. 32 (case 24).—Roentgenograms taken before operation and seven weeks, ten weeks, four months and fourteen months after operation. The photographs show the functional results ten months after operation.

temperature was 100 F. Pain was negligible. Suspension with 5 pounds of traction was used for five weeks after operation, then the patient was allowed to walk with a leather spica and crutches. The period of hospitalization was eighty-one days.

In October, 1930 (fourteen months postoperative), examination showed the patient to be walking with crutches but bearing almost full weight, without pain on the side on which operation had been performed. He could sit well back in a chair. Active motions were as follows: complete extension; flexion, 120 degrees; adduction, 15 degrees; abduction, 15 degrees; internal rotation, 10 degrees; external rotation, from 15 to 20 degrees. The passive motions were the same as the active.

Comment.—A particularly good result was obtained in view of the fact that there was nonunion of fifteen months' standing which was also complicated by poliomyelitis of the injured extremity. Roentgenograms showed bony bridges extending across the line of fracture, but union was not yet complete.

SUMMARY

The first twenty-four cases in which this method of treatment was used are here reported. In four, no end-result can be recorded for the following reasons:

In case 18 (see case records), the patient was discharged home at the end of two months. At that time the roentgenograms showed apparent beginning bony union. The patient lived some distance from the hospital and was unable to report for examination. At the end of five and a half months he died from cerebral hemorrhage. At the time of his death he was getting along well, being able to walk with crutches or a cane, but since we have no final roentgenograms we cannot classify the result as to success or failure.

In case 21 (see case records), the patient was discharged to the state infirmary six weeks after operation. Roentgenograms taken before discharge showed good position. The patient died six months postoperatively without any additional roentgenograms being made. "Neurosyphilis" was the cause of death. Again the available roentgenograms were taken too soon after operation to decide the question of bony union.

In case 22 (see case records), we undertook operation in the face of nonunion of two and one-half years' duration. The operation consisted in a reconstruction operation, the remains of the head being nailed on the shaft. Postoperative roentgenograms showed excellent relationship of head, shaft and trochanter. When the patient was last seen, five and a half months postoperatively, she had excellent function and was able to walk even without a cane, but she did use a cane most of the time. Roentgenograms five and a half months after operation did not clearly demonstrate bony union. The patient is now in an insane asylum without equipment for roentgenograms, consequently no end-result can be recorded.

In case 24 (see case records), operation was undertaken after fifteen months of nonunion. Fourteen months have elapsed since operation; the patient has excellent function, and the relationship of head and neck has not changed. The last roentgenogram showed definite bony bridges across the fracture line, but bony union is not as yet complete. We consequently prefer to classify this case as a case without an end-result.

The end-results of the remaining twenty cases are as follows: bony union, fifteen (75 per cent); nonunion, three (15 per cent), and deaths (from sepsis), two (10 per cent).

In the fifteen cases of bony union there was not only bony union but excellent functional results. In some of these cases, there is a certain amount of discomfort and stiffness because of hypertrophic changes. Two patients have marked limitation of motion (see reports of cases 20 and 23). The hypertrophic changes have been demonstrated by roentgenogram from the first and are interpreted as due to the original trauma causing the fracture.

The three cases of nonunion occurred during the first two years when the technic of the operation had not been developed to its present stage and when the efficiency of the method had not been definitely proved.

In case 3 (see case records), nonunion occurred in a woman of 60. Analyzing the postoperative roentgenograms, we find that the nail did not sufficiently penetrate the head. Furthermore, there was no evidence of impaction. Both of these errors have been eliminated in later cases.

In case 4 (see case records), the nail was removed three months after it was inserted. The roentgenogram was responsible for the removal of this nail. It showed the nail in close proximity to the joint surface, and it was feared that damage might come to the joint if the nail were left in. There had been no evidence of absorption about the nail, and the apposition of the fragments was excellent. If our experience had been more extensive, the nail would not have been extracted, and the fracture would probably have gone on to bony union; but, because of our lack of experience, we did not have the courage to leave the nail in. After removal of the nail, nonunion occurred.

In case 8 (see case records), postoperative roentgenograms showed absence of impaction but good relation of the fragments. At the time of operation the direction of the nail had to be altered. This additional trauma may have interfered with circulation sufficiently to account for nonunion. Other cases in which this error in technic was present have, however, gone on to union. In this particular case the neck was absorbed and nonunion resulted. Six months after the first operation, the nail was removed and a Whitman reconstruction performed. The patient has now a very good result from this procedure, but pain is present and she uses a cane.

There have been no immediate postoperative deaths in this series, but two patients died of sepsis. In case 9 (see case records), the patient did extremely well after the operation. She was 80 years old, the oldest patient in the series. For three weeks she had a normal temperature, but at the end of this time a superficial stitch abscess developed. Her resistance to sepsis was evidently low, for at the time of her death, one hundred and five days after operation, the infection had extended to her hip joint.

In case 15 (see case records), infection was in all probability hematogenous in origin. On the morning of the operation the patient had a temperature of 102.8 F. which was not called to the attention of the surgeon. This temperature was evidence of a general infection, which in the presence of the operative procedure produced local sepsis.

Our experience emphasizes the fact that older patients have a lowered resistance to infection and consequently every precaution must be taken to avoid sepsis. A hematoma is ideal soil for bacterial growth; consequently, hemostasis should be as nearly perfect as possible. This is a particularly important point when spinal anesthesia is used. With this type of anesthesia we have a temporary drop in blood pressure, and as a consequence bleeding is reduced to a minimum during the operation. When the blood pressure rises postoperatively, there is apt to be considerable oozing, resulting in a hematoma. To prevent this from happening, a compression spica is helpful.

Aseptic technic cannot be sufficiently emphasized in these cases. An unaccounted for temperature following any operation on the hip demands early exploration of the wound in the operating room.

The age of the patients was as follows:

20 to 30 years.....	2
30 to 40 years.....	2
40 to 50 years.....	2
50 to 60 years.....	9
60 to 70 years.....	7
70 to 80 years.....	1
80 to 90 years.....	1
Total	<hr/> 24

It is interesting to see from these statistics that the majority of the patients were between 50 and 70 years of age.

In four of the twenty-four cases nonunion was of longstanding, as follows: one case, ten months; one case, fifteen months; one case, nineteen months, and one case, two and one-half years.

In three of these cases of nonunion, bony union was obtained. In the fourth case, that of two and one-half years' duration, there was an excellent functional result when the patient was last seen, five and a half months after operation, but the bony union was questionable. This is one of the cases classified as having no end-result. The fact that bony union has been achieved in these cases of nonunion of long duration speaks well for the method.

CONCLUSIONS

In the treatment for joint fractures, anatomic reduction and early function are the two outstanding principles. Heretofore, the different methods of treatment for fractures of the neck of the femur have accomplished but one of these. Anatomic reduction has been achieved in the majority of cases, but early function has been impossible. The internal fixation of the fracture brought about by the three-flanged nail is absolute in all directions. Furthermore, it is a sustained fixation as well.

Because of this absolute, sustained fixation, postoperative immobilization is eliminated and early function is made possible. Early function means better chance of bony union and better ultimate function.

MEDIASTINAL EMPHYSEMA *

PARKE M. JESSUP, M.D.

FORT WAYNE, IND.

Consequences of Increased Mediastinal Pressure .

Effect on the Heart and Large Blood Vessels

Effect on the Trachea, Bronchi and Lungs

Effect on the Vagosympathetic Plexuses

Mechanism of Production and Report of Cases

Rupture of the Alveoli Without Injury to the Visceral Pleura

Trauma

Crushing Blows to the Chest Without Injury to the Wall of the Chest

Resuscitation of the New-Born

Expulsive Efforts During Labor

Accidents During Birth

Disease

Rupture of Lung and Visceral Pleura-Tension Pneumothorax

Trauma

Crushing Blows to the Chest With or Without Injury to the Thoracic Wall .

Perforation of the Lung by Foreign Bodies

Operative Wounds of the Lung

Disease

Artificial Pneumothorax

Injury to the Upper Air Passages

Operations in the Pleural Cavity Without Injury to the Lung

Sources of Mediastinal Air Other Than the Respiratory Apparatus

Operations at the Base of the Neck

Open Wound of the Diaphragm

Rupture of the Esophagus

Open Wound of the Intestinal Tract

Treatment

Summary and Conclusions

Mediastinal emphysema occurs much more frequently than the available literature leads one to believe. There are only a few cases reported in the English literature, and in these reports the significance of the complication is not emphasized. It is a complication that may present itself in a great variety of diseases. The mechanisms of production are numerous, but the symptoms produced are constant and

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significant. Many cases end fatally, the real cause of the severe symptoms often being obscure until revealed at autopsy. In some instances death can be avoided by early recognition of the condition and by the application of suitable treatment.

The clinical picture of mediastinal emphysema seems to be dependent on the effects of increased mediastinal pressure. Slight variations in the picture are probably due to nervous reflex impulses having their origin in the vagosympathetic plexuses. This point, however, requires further experimental evidence.

The cases herein reported demonstrate some of the various circumstances under which mediastinal emphysema can occur. One unusual case is reported—the result of an accident occurring during an operation on the upper part of the abdomen. I was not able to find another such case reported in the literature.

CONSEQUENCES OF INCREASED MEDIASTINAL PRESSURE

The term "mediastinal pressure" as used here refers to a diffuse pressure and not to localized pressure such as is caused by hemorrhage, abscesses, etc. A review of the reported experimental work and clinical cases, along with a study of some cases occurring in this hospital, has indicated that the effects of mediastinal emphysema are the result of increased mediastinal pressure.

EFFECT ON THE HEART AND LARGE BLOOD VESSELS

Jehn and Nissen¹ have shown that there are no noticeable outward changes until the intramediastinal pressure reaches about zero. After the pressure reaches zero, changes do occur and progress rapidly, depending on the amount of pressure and the rapidity of increase. The first change noted is that respiration becomes shallow and slightly quickened. Soon afterward there is a drop in blood pressure. They stated that any increase in mediastinal pressure can take place only by compression of some other intrathoracic structure. The elastic, easily compressed systemic and pulmonary venous walls are then the first to be affected. By compression of the systemic veins, the flow of blood to the right auricle is diminished. At the same time compression of the pulmonary veins diminishes the flow to the left auricle, thus producing congestion of the peripheral veins and congestion of the lungs. They found that by the injection of air it was possible to increase the mediastinal pressure from the normal minus 4 to plus 35 mm. of water and to get extreme changes in the animal; marked dilatation of the peripheral veins, severe dyspnea, a marked drop in blood pressure and

1. Jehn, W., and Nissen, R.: *Pathologie und Klinik des Mediastinalemphysems*, Deutsche Ztschr. f. Chir. **206**:221, 1927.

pulmonary congestion. Yet recovery took place if the injection was stopped. When more air was injected and death occurred, they found a constant picture at autopsy. The large veins were "pressed together" and surrounded with large bubbles of air. The loose areolar tissue of the mediastinum was greatly distended with air. The systemic veins were greatly engorged beyond the place where they enter the mediastinum. Changes were not noted in the contour of the arteries or of the trachea.

From a series of experiments, Achard² reported that many times, when air was injected into the mediastinum, large collections were found over the anterior surface of the pericardium. This, by its location and volume, considerably restricts the contractions of the heart as would a pericardial effusion.

Jehn³ reported a case which at autopsy revealed the heart compressed to such a degree that it contained no blood. The arteries and veins were empty; only the large veins of the body and the pulmonary veins within the lungs contained blood. These were greatly dilated with very dark blood.

EFFECT ON THE TRACHEA, BRONCHI AND LUNGS

According to Jehn and Nissen,¹ the changes in blood pressure are due to several factors. The initial fall in blood pressure is due to diminished filling of the left auricle, because the pulmonary veins are the first to be compressed. The secondary rise in blood pressure is temporary and due to increased respiratory efforts. When still more air is injected, there is a constant and characteristic drop in blood pressure, and an increase in pulse rate, because the vena cava is now compressed, and filling of the right auricle is hindered.

They stated that pulmonary congestion is an early finding in mediastinal emphysema, for the reason that air first collects in the niche of the aortic arch. The aorta is pushed to the left, thus making definite compression at the confluence of the pulmonary veins. Compression takes place here before any noticeable changes take place in the systemic veins; therefore, dyspnea is seen early. Dyspnea is caused by congestion and not by tracheal or bronchial compression. Even a high grade of mediastinal pressure does not compress the trachea.

Ballon and Francis⁴ were able to show essentially the same effects of increased mediastinal pressure by the use of a rubber balloon placed

2. Achard, C.: *Étude expérimentale de l'emphysème du médiastin*, Bull. Acad. de méd., Paris **80**:609, 1918.

3. Jehn, W.: *Ein Beitrag zur Klinik und Pathologie des Mediastinal-Emphysems*, Deutsche Ztschr. f. Chir. **140**:398, 1917.

4. Ballon, H. C., and Francis, B. F.: *Consequences of Variations in Mediastinal Pressure: Mediastinal and Subcutaneous Emphysema*, Arch. Surg. **19**:1627 (Dec.) 1929.

in the mediastinum. It was so arranged that they were able to inject or withdraw air at will. When air was injected, they recorded a marked drop in blood pressure and a decrease in respiratory amplitude. When the air was removed, both the blood pressure and the respiration quickly returned to normal. The arrest of respiration was here due to localized pressure on the trachea. In one instance, a rent occurred in the balloon and free air escaped into the tissue, with death to the animal. The observations at autopsy were essentially the same as those already mentioned.

EFFECT ON THE VAGOSYMPATHETIC PLEXUSES

It is possible that the increase in pressure may have some effect on the vagosympathetic nerve plexuses. Riedinger⁵ has shown that blows on the chest are followed by a fall in blood pressure in the carotids. The resulting disturbance in the circulation of the brain caused the respirations to become short and frequent. If the vagi were cut before the blows, the blood pressure did not fall. Breathing, however, became slow and deep, but after the cervical sympathetics were cut it became short and frequent.

MECHANISM OF PRODUCTION AND REPORT OF CASES

Air in an amount sufficient to cause an increase in mediastinal pressure can reach the mediastinum only by certain pathways. In the order of their frequency, these pathways are: (1) the pulmonary interstitial tissue, extending along the peribronchial and perivascular connective tissue to the hilus, thence diffusing into the loose areolar tissue of the mediastinum; (2) extension of a subcutaneous emphysema along the endothoracic fascia or the deep fascia at the jugulum; (3) the direct sucking of atmospheric air through wounds in the superior and inferior apertures of the thorax; (4) injury of the trachea and main bronchi whereby air is blown directly into the mediastinum; (5) openings in the mediastinal pleura so that air produced by pneumothorax is admitted, and (6) extension of retroperitoneal emphysema through the crus of the diaphragm.

When there is an infection of the tissues by gas-forming organisms, the gas may reach the mediastinum along one of the foregoing pathways.

Air may escape from the mediastinum in two ways: 1. It may be forced out through the diaphragm by following the tissues surrounding the aorta, thus forming a retroperitoneal emphysema which is most marked in the perirenal fat. 2. It may be forced out at the jugulum and produce a more or less widespread subcutaneous emphysema. A

5. Riedinger, F.: Concussion of the Chest, in Bergman and Bull: *A System of Practical Surgery*, Philadelphia, Lea Brothers, 1904, vol. 11, p. 371.

large quantity of air may remain in the mediastinum and not escape to other tissues, but usually some subcutaneous emphysema is present. If emphysema of the soft parts is present, it has several meanings:

1. Emphysema of the soft parts is seen in cases of simple fracture of the ribs with puncture of the lung, the air from the pleural cavity being forced into the soft tissues at the site of the injury to the parietal pleura. In these cases the emphysema is of little importance.

2. It is seen when a pneumothorax is formed by a perforating wound of the wall of the chest and atmospheric air passes into the pleural cavity and out into the intermuscular planes and subcutaneous tissues. In itself this type of emphysema is not grave.

3. When emphysema of the skin accompanies an increasing tension pneumothorax, with injury of the wall of the chest, and is becoming widespread, it can be of great importance, because eventually air will reach the mediastinum along fascial planes, the endothoracic fascia or the deep fascia of the neck.

4. When it is present in cases of rupture of the lungs with the wall of the chest intact, it has a definite meaning. The air can have reached the subcutaneous tissues only by way of the mediastinum.

5. Should there be emphysema of the soft parts without pneumothorax or rupture of the lung, it may be supposed that there has been a subpleural rupture of the alveoli.

RUPTURE OF THE ALVEOLI WITHOUT INJURY TO THE VISCERAL PLEURA

Extravasated air in the pulmonary interstitial tissue always results from the opening of bronchi or of alveoli. Subpleural rupture of the alveoli may take place to such a degree that there is an escape of air sufficient to reach the mediastinum. The rupturing occurs as a result of either a sudden increase of pressure within the alveoli, or else by a weakening of the alveolar wall. Kelman⁶ has demonstrated this experimentally. By introducing a cannula connected to a bicycle pump into the trachea of rabbits and thus suddenly increasing the intrapulmonary pressure, she produced a mediastinal emphysema without pneumothorax. Sections of the lung revealed ruptures of many of the alveolar walls and distention of the interstitial tissue with air. She was able to observe grossly that air collected in the peribronchial and perivascular tissue and that it bubbled out at the hilus. Furthermore, she was able to show that if rabbits were inoculated with the virus obtained from

6. Kelman, S. R.: Experimental Emphysema, *Arch. Int. Med.* **24**:332 (Sept.) 1919.

cultures of bacteria taken from patients with influenza, the alveolar walls became friable and burst more readily.

Trauma.—Crushing Blows to the Chest Without Injury to the Wall of the Chest: An acute increase in intra-alveolar pressure may take place if the wall of the chest is suddenly compressed at a moment when there is obstruction to expiration, as when the glottis is closed or a foreign body is present. A muscular straining effort or a spasm of coughing acts in the same manner. It may be assumed that rupture could result from too great positive pressure inhalations when employed to inflate a collapsed lung.

The following case from the literature exemplifies the foregoing type of trauma.

Bisshopp⁷ reported the case of a child, aged 4 years, who was run over by a cart, the wheel passing over the chest. There was immediate emphysema of the neck and face which rapidly spread over the entire body. The child was markedly cyanotic and dyspneic. The veins of the neck were greatly distended; the pulse was imperceptible. There was no evidence of fractured ribs or pneumothorax. Multiple incisions were made about the neck and upper part of the chest, and air escaped with a hiss. Improvement was prompt, and recovery took place. It was assumed that there was a subpleural rupture of many alveoli, and emphysema resulted from the extension of air along the bronchi to the mediastinum, thence to the subcutaneous tissue at the jugulum.

Resuscitation of the New-Born: Poeck⁸ reported two cases of asphyxia in new-born infants. Artificial respiration was given, and the infants were made to breathe, but soon a generalized emphysema appeared and death followed. Autopsy revealed many subpleural blebs, marked interstitial emphysema of the lungs and large collections of air in the mediastinum. The findings were explained by the fact that when artificial respiration was being employed, the lungs were squeezed at a time when the upper air passages were plugged with meconium, thus obstructing the outflow of air. Rupture of many alveoli resulted. When the infants started breathing, air continued to be extravasated into the interstitial tissues and thence to the mediastinum.

Expulsive Efforts During Labor: Klots⁹ described four cases that occurred during labor. They all developed during the second stage of hard labor, with either a large baby or a contracted pelvis. Diag-

7. Bisshopp: Extensive Emphysema from Passage of Cartwheel Over Thorax, *Brit. M. J.* 1:163, 1884.

8. Quoted by Stransky, E.: Beiträge zur Klinik des mediastinalen Emphysems durch Alveolarruptur im Säuglingsalter, *Monatschr. f. Kinderh.* 39:104, 1928.

9. Klots, P. S.: Emphysema subcutaneum während des Gebäractes-Entstanden, *Ztschr. f. Geburtsh. u. Gynäk.* 41:357, 1899.

nosis was made from the appearance of subcutaneous emphysema at the jugulum. The symptoms were mild, and recovery took place in all cases. The development of emphysema was explained by the fact that in order to bear down in an expulsive effort a deep breath was taken, the glottis closed, and thus the air in the lungs was put under great pressure. The alveoli burst and air escaped.

Jehn and Nissen¹ observed the same process in a patient following an unquiet narcosis, and also in the case of a schizophrenic patient at the beginning of an excited state.

Accidents During Birth: Kirschgessner⁸ saw subcutaneous emphysema in a new-born infant who, on account of a prolapse of the cord, was delivered by version. The infant was asphyxiated, but was eventually made to breathe. After it began to breathe, an emphysematous lump was seen at the base of the neck. The lump gradually receded and disappeared. The author explained the process as follows: First there was intra-uterine breathing, and then air was shut off during delivery. On account of the increased pressure in the lungs brought about by compression of the chest in the birth canal, an alveolar rupture occurred.

Disease.—Stransky,¹⁰ Levi and Catillon,⁸ Zarfl,¹¹ Ozanam,¹² Berkley and Coffen,¹³ Clark and Synnot¹⁴ and Wassermann¹⁵ have reported cases of mediastinal emphysema resulting from whooping cough, bronchopneumonia, influenza and diphtheria. The act of coughing is said to be the factor causing alveolar rupture in all these cases. After rupture has occurred, further coughing tends to drive more air into the interstitial substance and thus increases the degree of emphysema.

Kelman,⁶ in discussing a group of cases occurring during the epidemic of influenza of 1918, stated that alveolar rupture was partially due to the toxic effects of the infection, chiefly friability of the alveolar walls.

Gehrt¹⁶ reported four cases resulting from influenza in children. He also described a weakness of the alveolar walls which was due to

10. Stransky, E.: Beiträge zur Klinik des mediastinalen Emphysems durch Alveolarruptur im Säuglingsalter, *Monatschr. f. Kinderh.* **39**:104, 1928.

11. Zarfl, M.: Akutes mediastinales Zellgewebsenphysem und Hautemphysem bei einem 3 Monate alten Säugling, *Mitt. d. Gesellsch. f. inn. Med. u. Kinderh.* **4**:65, 1914.

12. Ozanam, C.: De la rupture pulmonaire chez les enfants, et de l'emphysème general qui lui succède, *Arch. gén. d. méd.* **3**:31, 1854.

13. Berkley, H. K., and Coffen, T. H.: Generalized Interstitial Emphysema and Spontaneous Pneumothorax, *J. A. M. A.* **72**:535 (Feb. 22) 1919.

14. Clark, E., and Synnot, M.: Influenza-Pneumonia Cases Showing Gas in Fascial Tissues, *Am. J. M. Sc.* **158**:219, 1919.

15. Wassermann, S.: Das mediastinale Emphysem, *Wien. klin. Wchnschr.* **33**:122, 1920.

16. Gehrt, J.: Hautemphysem und Stenose bei Grippe, *Deutsche med. Wchnschr.* **46**:1052, 1920.

bacterial toxins. He stated that in one case there was a severe tracheitis, the process extending into the bronchioles to such a degree that respiration was very difficult. In this case he thought that the alveolar rupture was due to the forced expiration.

Boehme¹⁷ observed the actual appearance of an emphysematous lump at the jugulum of an 18 months old child. The child had had bronchial pneumonia and was well on the road to recovery, when it was seized with a violent attack of coughing. Ten minutes later the lump appeared at the jugulum. Emphysema spread from this point and varied with the amount of coughing. By the free administration of sedatives to quiet the respiration, grave symptoms were averted, and gradual recovery took place. The explanation made was that there was a rupture of a bronchiole during the spasm of coughing.

Galliard¹⁸ reported a case in which emphysema developed in a patient with cholera. Before the emphysema appeared, the patient was already dyspneic. Death resulted, and at necropsy a marked mediastinal emphysema was found. A definite place in the right lung was found where the alveoli had burst, causing the condition. In a discussion of the case, it was stated that the mediastinal emphysema had resulted from the dyspnea and was not the cause of it.

RUPTURE OF THE LUNG AND VISCERAL PLEURA-TENSION PNEUMOTHORAX

Mediastinal emphysema may follow the entrance of air from a pneumothorax into the pulmonary interstitial tissue through a tear in the visceral pleura. When this happens, the course of the air is through the interstitial tissue to the hilus. It is possible that this air may extend along the main bronchi to the hilus of the opposite lung and spread peripherally to produce an interstitial emphysema of that lung. Then when a rupture of a subpleural bleb occurs, a contralateral pneumothorax results. The spread of the air in these cases is dependent not only on the tension but also on the continued escape of air from the pleural cavity into the extracostal tissue. As long as the tension can be kept at a minimum by the air infiltrating the subcutaneous tissue, it is not so likely to extend back through the lung. Another way by which tension pneumothorax air can reach the mediastinum is by breaking through the pleural reflexion at the hilus; or the air from the pleural cavity may be forced through a laceration in the parietal pleura and then along the endothoracic fascia to the mediastinum.

17. Boehme, G. F.: A Case of True Mediastinal Emphysema. *Med. Rec.* 95: 1052, 1919.

18. Galliard, M. L.: L'emphysème du médiastin, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1893, p. 199.

Trauma.—Crushing Blows on the Chest With or Without Injury to the Thoracic Wall: Trauma of this type may produce a rupture of the lung. When there is injury to the wall of the chest, namely, fracture of the ribs, the possibility of the lung being lacerated by a fragment of the rib is evident. However, Sauerbruch¹⁹ has shown that a rupture of the lung can result from crushing blows to the chest without fracture of the ribs. He was able to demonstrate this experimentally. After constricting the trachea of dogs, he placed a board across the chest and applied a sudden force. He found that rupture occurred at the point where the force was applied as well as in distant portions of the lung. He believed that the same thing happened in accidents to human beings. As a protective mechanism, the glottis closes at the end of inspiration; then pressure is suddenly applied to the chest, and the lung bursts. Sauerbruch believes that the accident is more common in children because of the great flexibility of the ribs.

Nissen²⁰ reported the case of a 9 year old girl who was run over by a truck. When first seen she had a marked subcutaneous emphysema over the entire body, more marked about the face and the neck. The symptoms were most distressing: decided cyanosis, dilatation of the superficial veins and rapid and irregular pulse. Tension pneumothorax was present on the left side; the pressures were + 13 and + 16 mm. of water. A valve drain was put in to relieve the tension, without a change in the condition. It was evident that something must be done to relieve the mediastinal pressure. An incision was made at the jugulum, and a finger was inserted into the upper part of the mediastinum. Air escaped with a hissing noise. Instantly the child's condition changed for the better. The valve drain was left in place, and the child recovered. As there was no fracture of the rib, the author assumed that there was a tear of a bronchus near the hilus brought about in the manner described by Sauerbruch.¹⁹

Sauerbruch¹⁹ reported the case of a man, aged 22, who was injured in an automobile accident. He was first seen shortly following the accident and was in a critical condition. His appearance was typical of that caused by mediastinal pressure. The second and third ribs were fractured anteriorly. Operation was performed in a negative pressure chamber at — 7 mm. of water. When the thorax was opened, the operator made the following interesting observations: "The collapsed lung was found lying against the mediastinum which was blown up like a cushion. The vena cava was seen to be as large as a child's

19. Sauerbruch, F.: Die Bedeutung des mediastinal Emphysems in der Pathologie Spannungspneumothorax, Beitr. z. klin. Chir. 60:450, 1908.

20. Nissen, R.: Die chirurgische Behandlung des bedrohlichen Mediastinal-emphysems, Zentralbl. f. Chir. 57:1023 (April 26) 1930.

arm, the azygos vein as large as a man's thumb. Upon incision of the mediastinal tissue the air escaped and the mediastinum assumed its normal proportions." A tear in the lung caused by a fragment of rib was repaired. The patient's condition rapidly improved, but three hours later all symptoms reappeared and death followed. Autopsy revealed a recurrence of the mediastinal emphysema, due to an imperfect closure of the wound in the lung.

An unusual point is brought out by Haim²¹ in a case in which death occurred three hours following an accident. Autopsy revealed a fracture of the seventh rib on the left, a fragment of which had punctured the left lung. There were a pneumothorax and a marked interstitial emphysema of the lung on the left side. On the right side, there was a partial pneumothorax without gross evidence of rupture of the lung. Haim²¹ stated that the emphysema spread from the left lung into the mediastinum at the hilus, thence across into the hilus of the opposite lung. The extension continued to the periphery, where a subpleural bleb ruptured, producing a contralateral pneumothorax.

Baranger²² described a case of rupture of the lung subsequent to fracture of the rib. Tension pneumothorax developed, and later signs of a mediastinal emphysema were evident. The mediastinum was opened at the jugulum, and a large amount of air escaped; a drain was left in the wound. The patient fully recovered.

In all of these cases air was presumably forced through the lung to the mediastinum.

Tiegel²³ reported the case of a man who had been struck with a heavy rod on the right shoulder. There were fractures of the third to the seventh ribs. Severe subcutaneous emphysema was present over the back, shoulders, neck and chest. At first the patient's condition was not alarming, but later the emphysema of the neck became extreme and his condition suddenly became grave. As it was thought that the emphysema had extended into the mediastinum at the jugulum, an incision was made in the neck. A suction cup attached to a water pump was applied to the wound. The results were immediate and excellent. Suction was maintained for several days, and the patient completely recovered. In this case it was thought that the air escaped from the wound in the parietal pleura and after distending the muscular structures of the back and neck it spread along fascial planes to enter the mediastinum at the jugulum.

21. Haim, E.: Ueber penetrierende Thoraxverletzungen, *Deutsche Ztschr. f. Chir.* **79**:269, 1905.

22. Baranger, M.: Un cas d'emphysème médiastinal traumatique, *Bull. et mém. Soc. nat. de chir.* **52**:1243, 1926.

23. Tiegel, M.: Ein einfaches Verfahren zur Bekämpfung des Mediastinal-Emphysems, *Zentralbl. f. Chir.* **38**:420, 1911.

The succeeding two cases occurred in this hospital.

CASE 1.—A white man, aged 54, was admitted to the hospital on Nov. 10, 1929, twelve hours following an automobile accident. Examination revealed that the patient was in considerable pain, which was made worse by respiratory movements. There was no cyanosis, and he was not dyspneic. There was subcutaneous emphysema over the entire chest, more marked on the left side. Signs of a left pneumothorax were present. Roentgen examination revealed pneumothorax on that side and fractures of the left clavicle and of the second to the sixth ribs posteriorly. The patient was put to bed, and sufficient narcotics were administered to keep him comfortable. There was little change in his condition

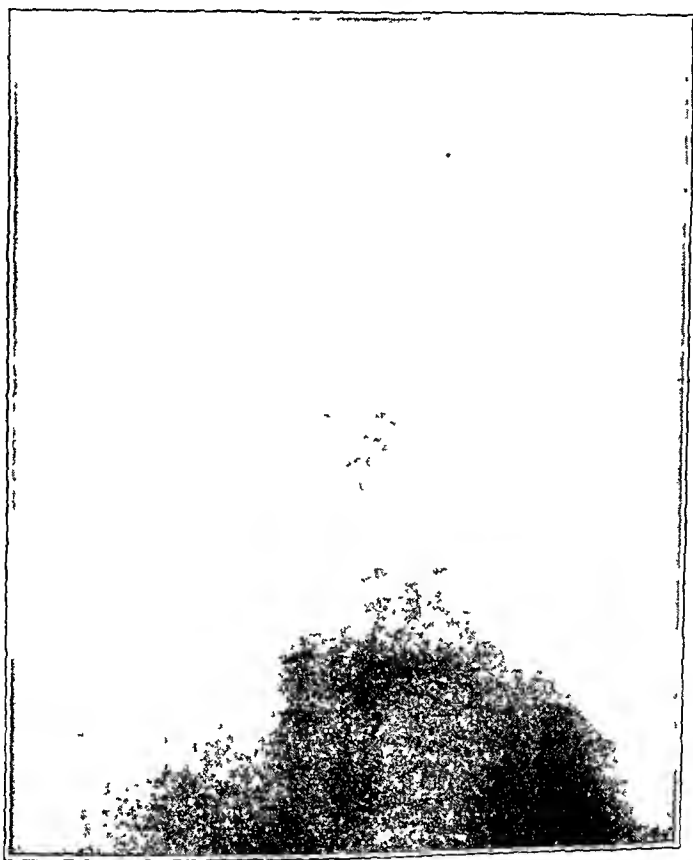


Fig. 1 (case 1).—Emphysema of the soft parts of the wall of the chest accounts for the extracostal blotchy shadows, and the radiating shadows in the pectoral regions are due to collections of air in the bundles of muscle fibers. There may be seen fractures of the left second to the seventh ribs at their angles. Pneumothorax is apparent on the left side. The mediastinal shadow is definitely widened, and its lateral borders are irregular. Light streaks, presumably air, may be seen running vertically through the dark shadow of the upper part of the mediastinum.

during the night and the following day. Early on the night of November 11, there was a definite change in the general condition. The patient became restless, dyspneic and cyanotic. The pulse rate was 120; the respiratory rate, 38. The subcutaneous emphysema was now seen to be decidedly increasing, and a large crepitant lump was felt and seen at the jugulum. Three hours later the dyspnea

had become more marked, and the general condition was quite alarming. As tension pneumothorax was now evident, a needle was inserted into the left pleural cavity. The initial pressures were $+16$ and $+4$. Large amounts of air were repeatedly aspirated during the next twelve hours, with little alteration in the patient's condition. The emphysema continued to spread, the cyanosis increased, and the dyspnea became more marked; death occurred early on the morning of November 13.

Autopsy showed the anterior mediastinum to be markedly distended with air. The left pleural cavity contained a large amount of air and a moderate amount of serum. The left lung was collapsed but was held to the lateral wall of the chest at one point by adhesions. There was a rent in the lung caused by a spicule of bone from the fracture of the seventh rib. The interstitial tissue of the left lung was markedly distended with air. The right lung was normal except for a pronounced venous congestion.

It is believed that in this case air from a pneumothorax first escaped into the subcutaneous tissue. Late in the second day the patient's condition became serious when presumably a tension pneumothorax developed and air began to infiltrate the ruptured lung and extend to the mediastinum. This was evidenced by the appearance of the emphysema at the jugulum coincident with the patient's change for the worse.

CASE 2.—A white man, aged 47, was admitted to the hospital on Dec. 14, 1928, following an automobile accident. When first seen, he was in a dying condition. The entire chest was tympanitic to percussion and was distended far beyond its normal size by subcutaneous emphysema. Dyspnea was extreme. Roentgen examination revealed multiple fractures of the second to the seventh left ribs, inclusive; the heart and mediastinum were shifted to the right. An attempt was made to decompress the tension pneumothorax, but on the insertion of the needle respiration ceased.

Autopsy showed both lungs to be widely separated in the anterior mediastinum by the distended air-containing mediastinal tissue. The left pleural cavity contained a large amount of air and a small amount of bloody fluid. The left lung was atelectatic and dull purple, with two puncture wounds in the upper lobe. The lower lobe was extremely congested and contained two puncture wounds. The right pleural cavity contained a small amount of air. The right lung was markedly congested, without gross evidence of rupture. Both lungs showed interstitial emphysema.

This case demonstrates the point shown by Haim.²¹ There were injury to one lung and a tension pneumothorax on that side, with interstitial emphysema of both lungs and a partial pneumothorax on the opposite side without gross evidence of rupture of this lung or of a tear across the mediastinum to account for the escape of air into the pleural cavity.

Perforation of the Lung by Foreign Bodies: Perforation of the lung by bullets, daggers, etc., as well as by fractured ribs in which the fracture is compound, differs from that described only in that there is a communication between the pleural cavity and the atmospheric air.

As a result of the perforation of the wall of the chest, a tension may result from a sucking of air at this point.

During the World War, Jehn³ recorded the case of a German infantryman who was wounded in the side of the chest by a piece of stone that was blown into the lung. He was first seen twelve hours following injury, with an extensive emphysema of the neck, chest and head. There were no serious respiratory or cardiac symptoms. Twelve hours later the clinical picture suddenly changed, and mediastinal



Fig. 2 (case 2).—There is marked emphysema of the soft parts of the wall of the chest and the neck. Fractures of the second to the seventh ribs posteriorly are seen. There are a definite pneumothorax on the left side and a partial one on the right. The heart has been decidedly shifted to the right. The vertical streaks seen just lateral to the vertebral column are probably the collections of air between the parietal pleura and the bodies of the vertebrae.

emphysema was suspected. An incision was made at the base of the neck, and there was an escape of a large amount of air which temporarily relieved the patient, but death soon followed. Autopsy revealed a much distended mediastinum and dilated peripheral veins. The injured left lung had a lacerated tract leading to the lower lobe and contained

much destroyed tissue and coagulated blood. In the center of the mass of lacerated tissue and blood clot was found the open stump of a large bronchus, which had been severed by the bit of stone. At first the air from this open bronchus was blown out through the pathway made by the missile, but after coagulation had closed this pathway, the escaping air passed through the peribronchial tissue to the hilus. The author stated that the rapid spread of air to the mediastinum accounted for the patient's sudden death.

Operative Wounds of the Lung.—These wounds provide yet another possibility. Sauerbruch¹⁹ observed a case in which, following lobectomy and ligation of the large bronchi, a bronchus reopened secondarily and retracted into the hilus. Air was blown directly into the mediastinum.

CASE 3.—A white girl, aged 7 years, was admitted to the hospital with an abscess of the right lung. She appeared to be very ill. The white blood count was 27,000; the temperature was 104 F. Roentgen examination showed a circumscribed area of density in the lower part of the upper lobe of the right lung. On Nov. 9, 1930, a first stage operation for drainage was performed. The post-operative condition was satisfactory. On November 15, a second stage operation was done. The pleurae were found adherent. A finger was inserted into the abscess cavity, which was found to be about 8 cm. in diameter and to lie against the angles of the ribs. The cavity communicated with a large bronchus. In order to make the drainage more complete, a section of the sixth rib was resected at its angle, and the pleura were incised. Adhesions had not formed at this point, and when air was admitted to the pleural cavity, the lower lobe of the lung was seen to move violently with respiration. The abscess cavity was opened posteriorly, and the lung was then inflated with positive pressure. A gauze pack was introduced to occlude the posterior operative wound, its anterior end being brought out at the axillary wound. Both wounds were closed tightly. Before the patient left the operating room, there was considerable emphysema around the posterior wound. For the first eight hours the patient's condition was not alarming; the emphysema spread very little. Early the same night the emphysema began to spread, and the anterior regions of the neck became greatly distended. The patient became cyanotic; the respirations were rapid and heaving, and the pulse rate increased. Oxygen did not relieve the cyanosis. The patient died early on the morning of November 16. Permission for necropsy was not obtained.

It is assumed that the air from the open bronchus in the abscess cavity gradually forced its way into the extracostal soft parts. This in itself caused the patient no serious trouble. As the posterior wound was close to the mediastinum, the air gradually found its way along the endothoracic fascia and entered the mediastinal tissue. This was evidenced by the appearance of the discrete emphysematous lump at the jugulum. When the air appeared at the base of the neck, the patient's condition became serious and death soon followed.

Disease.—The most frequent causes of spontaneous tension pneumothorax are rupture of tuberculous cavities, emphysematous blebs and nontuberculous suppurative tissue.

Pick²⁴ reported a case of cavernous pulmonary tuberculosis in which the patient received treatment by artificial pneumothorax. On one occasion an accident occurred during the administration of air. Death was the result. At autopsy it was found that the pleurae of the upper lobe on one side were adherent, and immediately beneath this area there was a large cavity. The pressure from the pneumothorax had caused the cavity to rupture through the adherent pleurae, and thus intrapulmonary air escaped into the deep tissue at the dome of the hemithorax. The entire mediastinum soon filled with air.

CASE 4.—A white man, aged 21, was admitted to the hospital on Sept. 4, 1929. The diagnosis of pulmonary tuberculosis had been made on a previous admission. At this admission the patient had the clinical and roentgen findings of a spontaneous tension pneumothorax. There were marked respiratory difficulty and slight cyanosis. The pulse rate was 140; the respiratory rate, 40. There was a definite shift of the mediastinum to the left. When the needle of the pneumothorax apparatus was inserted, the initial readings were + 16 and + 12 mm. of water. After 9,600 cc. of air was withdrawn, the pressures were + 5, — 1. It was obvious that the pressure was rising as fast as air was removed. A valve drain was left in the pleural cavity. Respiratory embarrassment after this was slightly relieved, and the pulse rate became slower and of better quality. On the morning of September 5, subcutaneous emphysema was noted about the upper part of the right side of the chest, anteriorly. The general condition was somewhat improved; the pulse rate was 128, and the respiratory rate, 30. By evening of this day, the emphysema had spread. The right side of the chest, arm and neck was greatly distended. Cyanosis was more marked. The intrapleural pressures were + 18 and + 12. Twelve hundred cubic centimeters of air was taken out. On September 6, the emphysema had spread over the entire right side of the body; cyanosis was more evident, and the respirations were more labored. More air was withdrawn, but without relief. The administration of oxygen was started, which improved the cyanosis. On the morning of September 7, a large emphysematous lump was noticed at the jugulum, and all of the symptoms were much more pronounced. During the day, the emphysema spread over the left side of the body and grossly distended the face. Oxygen did not affect the cyanosis. During the next day, there was little change in the patient's condition, but on September 9 the general emphysema was seen to be much increased, the entire body being inflated. The pulse rate was more rapid and thready, and there was a definite fall in blood pressure. Air was withdrawn from the pleural cavity until the pressures were — 6 and — 2, but the symptoms were not altered. Death occurred on the morning of September 10.

At autopsy the right pleural cavity was found to contain a great amount of free air and fluid. The left pleural cavity was normal. The mediastinal tissues were greatly distended with air, separating the borders of the lungs in the midline for about 12 cm. The left lung was much congested and contained active tubercles. The right lung was collapsed and dull purple. In the upper lobe there were three patches of adhesions which had become detached from the parietal pleura when the pneumothorax occurred. The right lung was inflated under water, and it was found to have a tear in the visceral pleura of the upper lobe.

24. Pick, E.: Ueber einem Fall von Haut und Mediastinal-Emphysem bei Lungentuberkulose, Wien. klin. Wchnschr. 38:508, 1925.

This slitlike tear had a flap valve arrangement. Immediately beneath this tear was a cavity measuring about 2 cm. in all dimensions. Three small bronchi opened into this cavity.

It will be noted that in this case symptoms were severe from the onset, but they were relieved by lowering the tension of the pneumothorax. On the day that the emphysema appeared at the jugulum, all of the symptoms became more marked and nonremittent. Oxygen did not relieve the dyspnea or alter the degree of cyanosis. The withdrawal of

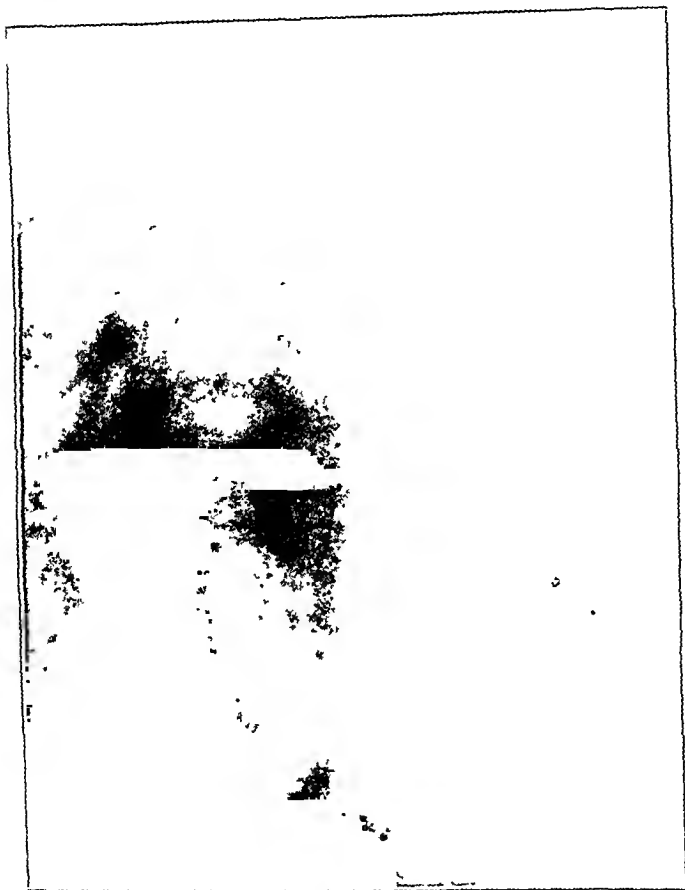


Fig. 3 (case 4).—Air may be seen in the subcutaneous tissues of the neck and the upper part of the thorax. The complete pneumothorax on the right side and the herniation of the small collapsed right lung into the left hemithorax are evident. The heart, trachea and all of the mediastinal structures are definitely shifted to the left. The right side of the diaphragm is markedly depressed. The mesial borders of the lungs are widely separated, and in the intervening shadow there are streaks and blotches which are probably collections of air in the mediastinal tissues.

air did not improve the patient's condition. Presumably, air escaped from the pleural cavity into the muscular planes of the chest through the injury in the parietal pleura made by the separation of the adhesion.

When the surrounding tissue had filled with air and the air was extending along different planes, it found its way along the endothoracic fascia to the mediastinum. Then there was a decided change in the patient's condition, which took place on the same day that the isolated lump appeared at the jugulum.

ARTIFICIAL PNEUMOTHORAX

Artificial pneumothorax presents a slightly different phase in the production of mediastinal emphysema. An accident that occasionally occurs is the insertion of the needle into the substance of the lung, thus allowing the inflowing air to follow the same path through the interstitial tissue as has been discussed elsewhere. Other accidents are tearing of the visceral pleura, or rupture of the superficial cavities by the needle. Another possibility to be considered is that in the evulsing of a phrenic nerve in the presence of a pneumothorax, the mediastinal pleura may be torn and the intrapleural air may thus enter the mediastinal tissue.

Sercer and Péčić²⁵ reported the case of a patient with chronic pulmonary tuberculosis whom they treated by artificial pneumothorax. Following the administration of air, on one occasion, a marked generalized emphysema occurred, which was soon followed by the death of the patient. It was stated that the patient had had five punctures in the right side posteriorly, and 600 cc. of air was given. At necropsy it was found that the lung had been punctured by the needle and a tension pneumothorax had resulted. They found that the air had escaped through the puncture holes in the parietal pleura and had extended along the endothoracic fascia to enter the mediastinum and distend it to great dimensions.

Parfaitt and Crombie²⁶ reported a case of mediastinal emphysema as a result of artificial pneumothorax. They saw the condition fifteen times, but no fatalities were reported. The only symptoms were slight substernal pain, slight swelling and crepitation at the jugulum, which usually disappeared within thirty-six hours. They assumed that the accident happened either by misplacing the needle point into the lung or by producing a fissure in the visceral pleura and thus making a communication between the interstitial tissue and the intrapleural air.

It is significant to note that when the flow of air extending into the mediastinum is not continuous or the amount accumulative, the symptoms are not severe.

25. Sercer, A., and Péčić, R.: Ein Beitrag zur Kasuistik Todesfälle beim künstlichen Pneumothorax, *Beitr. z. Klin. d. Tuberk.* **53**:123, 1922.

26. Parfaitt, C. D., and Crombie, D. W.: Five Years' Experience with Artificial Pneumothorax, *Am. Rev. Tuberc.* **3**:85, 1919-1920.

INJURY TO THE UPPER AIR PASSAGES

It is evident that when perforating injuries of the trachea, larynx or main bronchi occur, air may be blown directly into the mediastinum, and rapidly distend it.

Jehn²⁷ reported a case of mediastinal emphysema resulting from a fracture and perforation of the larynx, the air being forced from the larynx into the deep tissue of the neck and extending into the mediastinum. Incision was made in the neck to allow an escape of air, and the patient improved, but later he died of acute mediastinitis.

CASE 5.—A white girl, aged 16, was admitted to the hospital. She was pregnant at full term and went into labor on Nov. 29, 1927. At 9:40 p. m. she was taken to the delivery room, and ethylene anesthesia was started. At 10:10 p. m. an explosion occurred. The patient partially rose from the table, then fell back and began coughing large amounts of foamy blood. A few minutes later the patient's neck became swollen with emphysema, and the superficial veins became engorged and prominent. The emphysema spread with great rapidity, and the respiration soon became dyspneic. It was thought that blood had clotted in the trachea, and a tracheotomy was done to favor the respiration. The pulse became very rapid but was of fair quality; the cyanosis and dyspnea increased. The patient died at 11:00 p. m.

Postmortem examination explained the cause of the rapid appearance of the emphysema and its speedy extension. Just below the bifurcation of the trachea in the right bronchial wall there was a jagged hole about 1 cm. in diameter. This had apparently been caused by the impact of the explosion. There were no other gross injuries to the air passages or the lungs. Both lungs were markedly congested.

OPERATIONS IN THE PLEURAL CAVITY WITHOUT INJURY
TO THE LUNG

Operative procedures in the pleural cavity, not involving the lung, may be the cause of a mediastinal emphysema.

CASE 6.—A white man, aged 56, was admitted to the hospital on June 30, 1929. A diagnosis of mediastinal tumor was made. Operation was performed on July 1. A section of the second rib on the right side and cartilage were removed, and the parietal pleura was opened. The tumor was found to lie on the sides of the bodies of the second, third and fourth vertebrae. The pleura was incised all around the tumor, and the tumor was enucleated. The bed of the tumor was left bare of parietal pleura. The lung was then inflated, with positive pressure through the anesthetic mask. Air-tight closure of the wound in the anterior wall of the chest was difficult. The patient's immediate postoperative condition was good. In the evening of that day the patient became slightly dyspneic, and subcutaneous emphysema developed around the wound. There was little change in his condition until late the following day. The dyspnea became more marked; he was cyanotic, and the emphysema was rapidly increasing. The pulse rate was 120 and of poor quality; the blood pressure was 90 systolic and 70 diastolic. Roentgen examination showed complete pneumothorax. Air was aspirated, and

27. Jehn, W.: *Das Mediastinal-emphysem*, Zentralbl. f. Chir. 48:1619, 1921.

the pressures were reduced from $+6$ and $+2$ to $+2$ and -7 . His condition slightly improved. An attempt was made to seal the wound in the skin. All of the symptoms soon became more marked, and death occurred early on the morning of July 3.

At necropsy, the right pleural cavity was found to contain a large amount of air and fluid. The mediastinal structures were shifted to the left of the midline. The borders of the lungs were separated 8 cm. in the midline, and the mediastinal tissues were greatly distended with air. The veins of the neck and brain were dilated and very dark. The right lung was completely collapsed. The left lung contained air, but was markedly congested. The lungs were inflated under water, but did not show signs of a leakage of air.



Fig. 4 (case 6).—There is moderate emphysema of the soft tissues in the pectoral regions. There is a pneumothorax on the right side and a marked shift of the heart and entire mediastinum to the left. The mesial border of the left lung is pushed far over to the left. Vascular markings of the left lung are prominent. There is a decided widening of the mediastinum, most of the shadow being seen to lie in the left hemithorax. Streaks and patches of air are seen chiefly within the middle and upper parts of the mediastinum.

In this case a tension pneumothorax was formed by the sucking of air through the wound in the wall of the chest. The subcutaneous emphysema was a result of the air being forced from the pleural cavity into the tissues adjacent to the wound. The air entered the mediastinum by extending through the denuded area at the site of the tumor.

SOURCES OF MEDIASTINAL AIR OTHER THAN THE
RESPIRATORY APPARATUS

Operations at the Base of the Neck.—Under some circumstances air may enter the mediastinum through wounds of the neck. This occurs chiefly because of the negative pressure within the mediastinum. The most common occasion is found following thyroidectomies in which there has been removal of substernal portions of the gland, even without accidental tearing of the pleura. When the planes of fascia leading into the superior mediastinum are opened and there is forced inspiration, air may be sucked in and trapped in the spongy substernal tissue. This is especially true when there is tracheal compression causing inspiratory dyspnea.

Jehn and Nissen,¹ Gold,²⁸ and Buford²⁹ have reported cases of mediastinal emphysema following thyroidectomy. In several of the cases the cause of death was attributed directly to this factor. In the case reported by Buford,²⁹ the patient recovered after a very stormy postoperative course. The operator recognized the condition, knowing that air was sucked into the wound at the time of operation. The treatment employed was unusual in that venesection was done.

Open Wound of the Diaphragm.—If the diaphragm is perforated, air may be sucked into the inferior mediastinum. The following case was observed in this hospital.

CASE 7.—A white man, aged 23, was admitted to the hospital on April 30, 1930. A diagnosis of splenic anemia was made, and splenectomy was performed on June 16. A left rectus incision was made from the margin of the rib downward 9 inches (22.86 cm.) and then carried laterally. A rather large spleen was found; it was very adherent, and many large dilated veins coursed from it. An attempt was made to enlarge the incision upward; the diaphragm was accidentally incised in the midline. Immediately sucking was noticed in this wound; it was closed with a suture. This stopped the sucking. The spleen was removed with only a moderate loss of blood. The splenic bed was packed and the wound closed in layers about this packing. The immediate postoperative condition was poor. The pulse rate was 160; the respiratory rate, 44. (The change in pulse and respiration did not take place until the diaphragm was opened, when both sharply increased.) The patient soon became extremely cyanotic and dyspneic. A transfusion of whole blood was given, and dextrose was administered intravenously, but there was little change in the condition throughout the day. On the morning of June 17, another transfusion was given. Oxygen was administered but did not alter the extreme cyanosis. The pulse rate remained about 150 during the day; the respiratory rate remained above 40. There was definite distention of the veins of the neck. The symptoms gradually became worse, and death occurred late in the afternoon.

At autopsy evidence of postoperative hemorrhage or infection was not found in the abdomen. Neither pleural cavity contained free air or fluid. The borders

28. Gold, E.: Ueber Mediastinal-emphysem nach Strumektomie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **37**:352, 1924; Arch. f. klin. Chir. **138**:195, 1925.

29. Buford: The Entrance of Air into the Mediastinum During Operations on the Base of the Neck. Surg., Gynec. & Obst. **26**:540 (May) 1918.

of the lungs were widely separated in the midline. The mediastinal fat and areolar tissue were distended with air. The large veins entering the mediastinum were much distended and very dark. Both lungs were markedly congested, but there was no evidence of frank pneumonia.

Undoubtedly the patient's death was directly due to the emphysema of the mediastinum. All symptoms were characteristic of those due to increased mediastinal pressure. His condition changed little from the time the air entered the mediastinum until death. The probability is that the air was drawn into the mediastinum and was trapped there when the wound in the diaphragm was closed. The amount was sufficient to cause an interference with circulation, and the absorption of the air did not take place rapidly enough to lessen the mechanical blockage of circulation before death occurred.



Fig. 5 (case 7).—*A*, roentgenogram of the normal chest, taken two days before operation. *B*, roentgenogram of the chest taken immediately after death. The increased width and the change in the lines of the lateral borders of the mediastinum are noticeable. Both lungs show evidence of vascular congestion. The same vertical streaking present in the other illustrations is also seen here.

Rupture of the Esophagus.—Another source of air is from a perforation of the esophagus.

Pearce³⁰ reported an interesting case of emphysema and death. Post-mortem examination showed that there had been a rupture of a small abscess cavity in the wall of the esophagus close to the cardia of the stomach. There was a sinus tract leading from this abscess cavity, burrowing along beneath the mucous coat of the esophagus and opening

30. Pearce, W. H.: An Unusual Case of Emphysema, *Lancet* 2:1221, 1886.

into the stomach. When the abscess ruptured, gas from the stomach passed directly into the mediastinum, emerging at the jugulum and extending over the entire body. Also there was a small amount of free air in both pleural cavities. No explanation was offered as to the mechanism of formation of the bilateral pneumothorax.

Also gas from the gastro-intestinal tract may escape through wounds into the retroperitoneal tissue, and, passing through the crus of the diaphragm, may thus reach the mediastinum.

Open Wound of the Intestinal Tract.—Newman³¹ reported a case of generalized emphysema first appearing at the jugulum, following a rupture of the stomach. At autopsy marked pneumoperitoneum was found. The wall of the stomach was perforated; the opening had ragged edges, and there was a general abrasion of the surrounding wall of the stomach. There was great distention of the retroperitoneal tissue with air. Apparently the free air in the peritoneal cavity entered the tissues of the wall of the stomach at the place of rupture, then forced its way between the subserous and muscular coats, and finally reached the retroperitoneal tissue.

Erichsen³² saw a case of emphysema develop following puncture of the bladder through the rectum for relief from acute retention. The emphysema was noticed about the perineum and groins and at the base of the neck. The emphysema apparently reached the neck by extending along the tissues surrounding the great vessels to the mediastinum and thence to the surface at the jugulum.

TREATMENT

Treatment may be considered from two aspects: that of controlling the source of the air, and that of giving an outlet to the air already accumulated. In controlling the source of the air, surgical closure of a rent in the lung or the bronchus may be performed. Air-tight closure of sucking wounds should be made. Diversion of pneumothorax air to the exterior by the insertion of a valve drain may sometimes be sufficient. One method of making this valve drain is by fitting an 18 gage needle to a piece of rubber tubing, the distal end of which is immersed in a bottle of sterile water or boric acid solution, and placing it below the level of the thorax. When the needle is inserted into the pleural cavity, the air may be expelled through this water seal. An incision of the skin at the point where a subcutaneous emphysema is originating may prevent a rapid extension of the process. If labored respiratory movements are increasing the tension of a pneumothorax, the administration of narcotics for complete rest may be useful.

31. Newman, A. J.: General Emphysema Following Rupture of Stomach, *Lancet* 2:728, 1868.

32. Erichsen: Perineal Emphysema Spreading to Upper Parts of Body from Puncture of Bladder Through Rectum, *Lancet* 1:89, 1860.

Several cases of rapid recovery are reported in the literature following the incision of the skin about the neck, thus allowing the air to escape. The method of Tiegel²³ is unique in that he applied a suction cup over the incision in the jugulum and maintained a constant negative pressure.

SUMMARY AND CONCLUSIONS

By keeping in mind the circumstances under which mediastinal emphysema may occur and recognizing the symptoms when they appear, a diagnosis of the condition may more frequently be made.

The effects of mediastinal emphysema seem to be the result of increased mediastinal pressure. The outstanding effect is a mechanical interference to circulation brought about by the compression of the large veins entering both sides of the heart. Most of the outward signs observed are dependent on this blockage of circulation.

Air reaches the mediastinum by definite pathways, chiefly along fascial planes and through the tissues that are continuous with the areolar tissue of the mediastinum. Mediastinal emphysema has been known to result from injuries and diseases of the lung, from operations on the lung and also from perforations of the wall of the chest, operations in the pleural cavity and artificial pneumothorax. Perforating wounds of the larynx, trachea and bronchi have produced mediastinal emphysema. The mediastinum may suck air through wounds of the neck and diaphragm. Generalized emphysema from rupture of the esophagus has been reported; also, a retroperitoneal emphysema following a rupture of the stomach extended to the mediastinum.

The symptoms and physical signs are characteristic. Those most commonly present are extreme cyanosis and dyspnea, rapid pulse, congestion of the superficial veins of the neck and low blood pressure. Substernal discomfort and pain may be a complaint. Subcutaneous emphysema is usually present, but is not a requisite finding. Physical examination of the chest cannot be depended on. Usually signs are obliterated by the emphysema of the soft tissues. Tympany over the sternum is helpful. If the heart is surrounded by air, the sounds will be distant, and some observers have reported being able to hear emphysematous clicks synchronous with the contraction of the heart.

Roentgen findings are not characteristic but are helpful. Increased vascular markings of the lungs are often present. When the borders of the lungs are widely separated in the midline and when there are longitudinal dark streaks in the mediastinal shadow, this is suggestive of mediastinal emphysema. The borders of the lungs are separated because the mediastinum is distended. The dark streaks are thought to be due to the accumulation of air in the tissues along the great vessels and in the tissues between the parietal pleura and the bodies of the vertebrae.

All cases of crushing injuries to the chest with a spreading emphysema must be considered as potential cases of mediastinal emphysema. This possibility must be borne in mind also during certain operative procedures, and care must be taken to avoid the complication.

THE LYMPHATIC VESSELS OF THE THYROID GLAND IN THE DOG AND IN MAN*

WILLIAM FRANCIS RIENHOFF, JR., M.D.

BALTIMORE

The lymphatics of the thyroid have been referred to as the ducts of the gland. This reference originated in 1836, when King and Cooper¹ claimed to have observed colloid in the lymphatic vessels within the thyroid and also as they left the gland. Since that time the lymphatic drainage of the thyroid has been the subject of a great deal of controversy. This difference of opinion has arisen mainly because with the customary technic of injecting the lymphatics of parenchymatous organs by needle puncture there was uncertainty as to which channels have been injected—lymphatics, capillaries or tissue spaces. There is now a general agreement on the fact that the external surface of the thyroid is covered by a rich anastomosing plexus of lymphatic vessels and on the course of the larger extraglandular collecting trunks that drain the plexus. However, the relation of the lymphatic capillaries to the definitive histologic unit of the thyroid, i. e., the follicle, and the intraglandular pattern of the lymphatic system of this gland are the main controversial points which up to the present have remained undisclosed. This question seemed insoluble with the technic employed in the past. It was my purpose in this investigation to determine the fine terminal distributions of the lymphatic vessels of the thyroid of the dog and the intraglandular lymphatic plexus as revealed by a centripetal injection into these channels at a point removed from the gland. A comparative study has also been made of the human thyroid as well as of that of the cat and the guinea-pig.

HISTORY

The lymphatic system of the thyroid has attracted the attention of many observers in the past, and it may be well to mention the more important of these investigations and their contributors. Frey,² in 1863, described the lymphatic channels of the thyroid as having their beginning

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* From the Department of Surgery of the Johns Hopkins University and the Department of Embryology of the Carnegie Institute of Washington.

1. King, T., and Cooper, A.: Observations on the Thyroid Gland, Guy's Hosp. Rep. 1:429, 1836.

2. Frey, H.: Die Lymphbahnen der Schilddrüse. Verhandl. u. Mitt. Deutsche Klin. 15:478, 1863.

in blind alleys, cecum-like in form, between the follicles. Boechat,³ in 1873, reported his observations of shell-shaped lymphatic spaces or sinuses placed between the acini; these spaces were lined with a continuous layer of endothelium and traversed by septums of connective tissue or trabeculae to prevent excessive dilatation. In 1874, Navalichin,⁴ found that the follicles of the thyroid gland are not contiguous with the connective tissue stroma, but are separated from this tissue by lymphatic spaces, so that each follicle is lying by itself in a lymph lacuna, the blood vessels of the gland being surrounded by similar spaces which are drawn out more lengthwise. When an injection was made into the gland by direct puncture, the mass filling the space around the follicles and around the blood vessels in the connective tissue stroma flowed out; it then collected under the glandular capsule, which consisted of connective tissue, and finally entered the lymphatic vessels which leave the hilus and extend into the superior and inferior lymphatic glands of the neck. When a solution of 0.5 per cent silver had been injected, it became evident that the described lymphatic spaces of the thyroid were lined with a single layer of epithelium. The blood vessels lying within these lymphatic spaces were likewise covered with single layers of epithelium. From these observations, Navalichin drew the conclusion that the system of lymphatic vessels of the thyroid was perivascular. Baber,⁵ described a plexus of lymphatics close to the acini which varied in caliber but did not form sinuses. Zeiss,⁶ in 1877, and more recently Williamson and Pearse,⁷ in 1930, observed large cavernous or sinus-like lymphatic spaces which embrace usually one follicle or which may include two, four or six follicles, the lymphatic vessels leading off from these spaces accompanying the efferent and afferent blood vessels. To subscribe to the observations of Williamson and Pearse would necessitate the admission that the lymphatic system of the thyroid is an open one in communication with the tissue spaces between the follicles and blood capillaries. MacCallum⁸ was the first, in 1899, to

3. Boechat, P. A.: Les sinus lymphatiques du corps thyroïde, *Compt. rend. Acad. d. sc.* **76**:1026, 1873.

4. Navalichin, J.: Beobachtungen über das Lymphgefäß-System der Glandula thyreoidea und der Brustdrüse, *Arch. f. Physiol.* **8**:613, 1874.

5. Baber, E. Creswell: On the Lymphatics and Parenchyma of the Thyroid Glands of the Dog, *Quart. J. Micr. Sc.* **17**:204, 1877.

6. Zeiss, Otto: Mikroskopische Untersuchungen über den Bau der Schilddrüse, Strassburg, H. L. Kayser, 1877, vol. 8, p. 50.

7. Williamson, G. Scott; and Pearse, Innes H.: The Anatomy (Comparative and Embryological) of the Special Thyroid Lymph System, Showing Its Relation to the Thymus with Some Physiological and Clinical Considerations that Follow Therefrom, *Brit. J. Surg.* **17**:529, 1930.

8. MacCallum, W. G.: Die Beziehung der Lymphgefässe zum Bindegewebe, *Arch. f. Anat. u. Entwicklungsgesch.*, 1902, p. 273.

show in his studies of the lymphatic network of the skin in embryo pigs that the lymphatic system is a closed one. In this study he disproved the existence of communications between the lymphatic vessels and surrounding connective tissue spaces, called "Saft Kanälchen" by von Recklinghausen. MacCallum's original observations have since been confirmed by many studies of the lymphatic vessels of different regions and organs. Furthermore, as the conclusions of Williamson and Pearse were not founded on experimental injections into the thyroid but merely on conjecture, based, according to their own words, on examination of histologic sections of uninjected thyroid glands, it would seem necessary only to quote a passage from one of their recent articles in order to exclude their hypothesis:

The thyroid is the only gland in which under natural conditions the lymphatic system is found with great frequency to be active and distended with lymph and lymphocytes. The histologist therefore had not to await the results of injection and experiment to demonstrate the lymph system in the thyroid gland.

Each follicle of the thyroid lies in a lymph space so arranged that the epithelium of the thyroid is bathed directly by any lymph contained therein. Groups of such follicles with their perifollicular spaces are enclosed in a fibro-elastic capsule lined with endothelium. Within the limit of this lining the perifollicular spaces are continuous, forming slitlike channels running between the individual follicles. These channels are portions of the endothelial-lined sac rendered visible by fluid contents. It is to this endothelial sac with all its tortuous interfollicular channels that the name 'lymph sinusoid' is given. Each sinusoid, within which are packed columns of thyroid epithelium and a blood capillary plexus, represents one 'gland unit.' Groups of these encapsulated gland units are regularly clustered about a central lymphatic channel into which their sinusoids open freely. They are massed around the channel like grapes around a stalk. Each mass of gland units forms a lobule of the gland and is enclosed in a special compartment of the interstitia. This arrangement is analogous to that found in the lobule of the liver. The difference in structural arrangement between these organs is that that in the thyroid lymph takes the place of portal blood; lymph is as significant to the function of the thyroid as the portal blood is to hepatic function.

Matsunaga,⁹ in 1909, reported that the moderately broad lymphatic vessels coursing in the connective tissue layers which separate the follicles divide into a number of smaller branches which run along between several groups of the follicles and give off still finer divisions, which surrounded the single follicles. From these interfollicular lymphatic ducts, very fine lymphatic capillaries lead toward and into the interior of the follicles themselves, lying between the epithelial cells of the follicular wall, and are therefore to be looked on as "interfollicular" or "interepithelial" lymphatic ducts. The interepithelial ducts

9. Matsunaga: Die parenchymatösen Lymphbahnen der Thyreoidea und ihre Sekretion, Arch. f. Anat. u. Entwicklungsgesch., 1909, p. 339.

of the follicular wall run between the epithelial cells and terminate at the border between the colloidal contents and the inner epithelial edge.

Matsunaga discussed further the presence of intracellular ducts:

On the wall of a follicle is seen a cell with evident signs of nuclear degeneration and protoplasmatic vacuoleformation. It is into this cell that a lymphatic duct enters coming from a passing lymphatic vessel, while none of the other intact cells of the follicle wall show up any ducts. . . . It might be possible, that the intracellular lymphatic ducts do not develop and grow into the cells of the thyroid until these cells assume secretory activity, form vacuoles and begin to dissolve; and that from the first they are not present in the substituting cells. At the time of the secretory dissolution of the cells, open ducts would be available for the escape of the colloid or whatever substance is secreted from the inside of the follicles into the intracellular and wider lymphatic passageways.

He then concluded:

1. Between the interfollicular lymphatic vessels and the contents of the follicles there exists a communication by way of the intercellular lymphatic vessels of the follicle wall.
2. The cells of the follicle wall are gradually cast off, are transformed into the colloid, and this latter, or whatever are its essential ingredients, are excreted through the intercellular lymphatic ducts into the interfollicular lymphatic ducts.
3. Intracellular lymphatic ducts within the thyroidea probably do not commence to develop until the cell starts its secretory activity.

TECHNIC: MATERIAL AND METHOD

The thyroid glands used in this study were obtained from four of a series of forty dogs and also from ten persons with exophthalmic goiter on whom I operated in such a manner as to render the specimens suitable for injection, not only into the lymph but also into the blood vascular system. To accomplish this, one lobe of the thyroid was removed practically in its entirety by clamping all vessels well above or beyond their entrance to or departure from the gland. Thus the entire lobe, including both poles and the isthmus, were removed in one piece. The isthmus was clamped across so as not to allow the injected mass to run out. If any leakage occurred at the portion of the gland impinging on the tracheoesophageal angle, this region was also tied off and clamped. This was done so that enough pressure could be exerted on the syringe to insure complete injection of the lymphatics of the thyroid. Thus the lymphatic trunks entering and leaving the poles of the human thyroid were removed intact with the polar blood vessels. The thyroid of the dog was selected for study because in this animal the two glands are not connected by an isthmus, and at the same time the thyroid as well as the lymphatic vessels are of sufficient size to facilitate handling them readily. The thyroid glands of two cats and one guinea-pig were also injected, but since the observations of their glands and also of the human thyroid differed in no way from that of the dog, only the technic of injection employed in the latter and the results obtained will be described.

Advantage was taken of the fact that in the dog the right and left thyroid bodies are entirely separate, there being no isthmus or the remnant of one in the forty dogs of this series. In the beginning an attempt was made to employ retro-

grade injection in the thyroid by first ligating the large cervical lymphatic-collecting trunks of the neck. These were identified by injecting a 10 per cent solution of india ink into the superior cervical lymphatic glands on each side. The large descending cervical trunks quickly became visible as they rapidly filled with india ink, and they were ligated at several points along their course. Injection of india ink into these trunks, immediately or at hourly intervals up to forty-eight hours, in an attempt to inject the thyroid gland on that side, were unsuccessful because it was not possible to force the ink past the deep cervical glands which receive the lymphatic trunks from the superior pole of the thyroid. In many instances it was not possible to force the ink up through these large trunks to the superior cervical glands because of the valves. The reason for ligating these trunks was, of course, to allow the valves to become incompetent by ballooning out of the trunk with lymph. As this method proved unsuccessful, it was then thought that if all the draining lymphatic trunks from the thyroid were ligated on one side only, a collateral circulation might be effected which would enable one to inject the lymphatics of the ligated side and thus have the injected mass carried across the midline to fill the lymphatics of the opposite gland; in this way only the lymphatics of the gland on one side would be injected, there being no isthmus, and therefore no parenchymatous connection between the two glands. Most meticulous, careful ligation was made of all the efferent lymphatic trunks leading away from the left thyroid gland in dogs together with multiple ligations of the descending cervical trunk on the left side. This technic was carried out under general anesthesia with morphine and ether, and the most careful aseptic surgical technic was observed. After twenty-four hours, the dog was placed on his back, horizontally, on an operating table, and the left thyroid gland was exposed. With the dog on its back, the trachea is on a higher plane than the thyroid gland so that any fluid spilt will run down further on that side and not over the midline. A 10 cc. Luer syringe equipped with a no. 28 hypodermic needle was filled with 10 per cent solution of white label india ink. The needle was inserted into the parenchyma of the left thyroid gland just beneath the capsule and moved about slightly as the solution of india ink was injected. The surface lymphatic plexus of the left thyroid gland filled immediately, and it could be seen at a glance from the type and shape of the vessels that they were lymphatic channels. Considerable pressure could then be exerted on the plunger of the syringe, causing the surface lymphatics to become more or less distended or even overdistended. The lymphatic trunks leading away from the lower pole became filled as did those about the upper pole, and the drainage trunks leading to the superior cervical glands on the left were quite visible as well as the trunks draining toward the mediastinum. The ligatures in the pretracheal fascia, about the poles and lateral to the gland, prevented the ink from completely filling these trunks as their lumina was interrupted. With a continuation of steady pressure on the syringe, a very complex network of lymphatic vessels in a ribbon-like strand was observed to fill along the inner margin of the left thyroid gland and extend up and across the midline in the pretracheal fascia. This complex anastomosing narrow band of lymphatic vessels represented undoubtedly the ontogenetic vestige in the dog of the isthmus of the thyroid gland, and probably not a developed collateral circulation. The right thyroid gland was completely injected with the india ink, the lower pole of the gland injecting first with a gradual progression toward the upper pole. The large lymphatic trunks leading away from the lower pole on the right side were filled and visualized down to the superior mediastinal gland. The lymphatic trunks from the upper pole were filled, following a complete injection of the right gland, and carried the ink into the superior cervical glands on the right side (fig. 1).

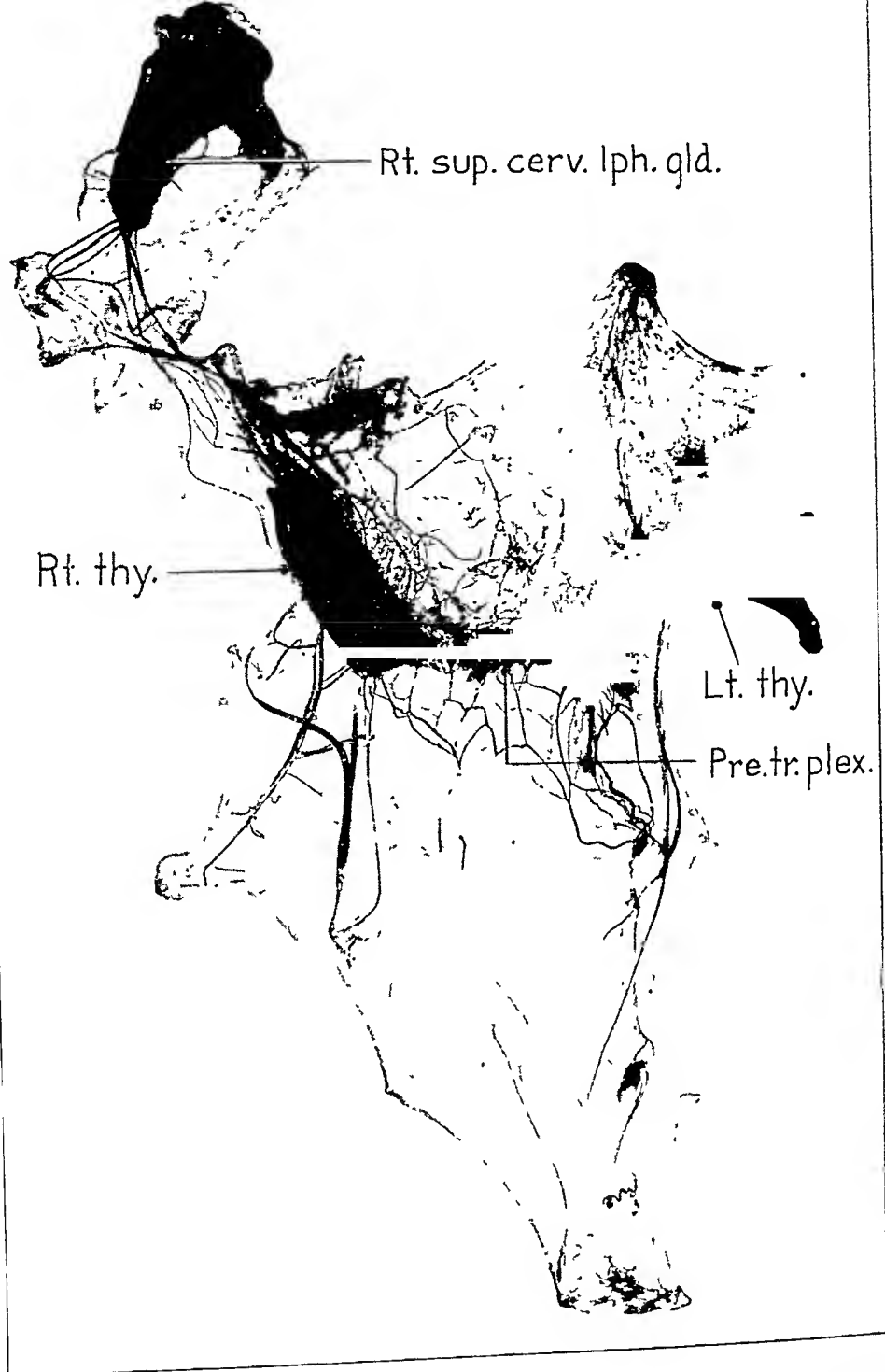


Fig. 1.—Photograph of a specimen of the right and left thyroid glands together with the right superior cervical lymph gland of dog 21 removed "en bloc" with pretracheal fascia; $\times 83$. The lymphatics were injected with a 10 per cent solution of india ink, the blood vessels with a modified solution of Gerota's prussian blue. Note the pretracheal lymphatic plexus with efferent lymphatic trunks draining down toward the mediastinum (*Pre. Tr. Plex.*). In the lower portion of the figure may be seen a small mediastinal lymph node. The characteristic pattern of the lymphatic trunks may be seen in this pretracheal plexus and also in the efferent trunks draining the superior portion of the right thyroid gland into the right superior cervical lymph gland. In the upper portion of the figure near the superior cervical lymph gland, the lymphatics have the appearance of chainlike links. On the inner margin of the right thyroid gland can be seen the injected superior thyroid artery. This, although injected with the solution of prussian blue, shows black in the photograph. The smooth contour of this vessel and the absence of the characteristic chainlike links is evident. At the inferior margin of the pretracheal plexus may be seen two small extravasations which are evidently different in their general appearance and contour from the lymphatic vessels. About the middle of the lower portion of the pretracheal fascia can be seen a small bladder-like structure connected with the lymphatics which may be an atypical

Thus the lymphatic vessels of the left thyroid gland were injected with a 10 per cent solution of india ink by a direct puncture into the gland. Following this injection, the ink was carried up and across the trachea in the midline by the lymphatic vessels of the pretracheal fascia. The maintenance of a constant head of pressure on the plunger of the syringe resulted in a complete injection of the lymphatic system of the right thyroid (figs. 1 and 2). A constant head of pressure



Fig. 2.—Higher magnification of the pretracheal plexus of the specimen shown in figure 1; $\times 3.6$. Note the characteristic appearance of the lymphatic vessels and the bladder-like absorbing unit at the lower portion of the photograph (*Abs. unit*). In the right side of the figure at the inferior margin of the pretracheal lymphatic reticulum can be seen three small extravasations the appearance of which is characteristic.

was estimated by the degree of distention of the lymphatic vessels forming the surface plexus over the left gland. The injection of the right gland was progressive from the lower pole to the upper, where the larger lymphatic trunks draining the upper pole of the gland were filled and carried the india ink into the

superior cervical glands (fig. 1). The entire parenchyma was injected before the superior lymphatic trunks were filled. As observed, the actual progression of the injected mass seemed to be first from the narrow lymphatic plexus across the midline into the surface network covering the lower medial aspect of the right thyroid from which the intraglandular network of lymphatic vessels were completely injected. Following this injection, the lymphatic vessels of the entire intraglandular plexus, the tributaries of the surface or extraglandular plexus of the remainder of the gland, were filled in succession, thus forcing the india ink into all drainage trunks of the superior and inferior poles of the gland. The right thyroid was transformed into a solid black mass. The dissimilarity between the narrow complex anastomosing band of lymphatic vessels, which extended across the midline, and the pattern of vessels resulting from the development of a collateral circulation was at once very evident (figs. 1, 2, 3 and 4).

The external carotid artery on the right side and then the one on the left were injected with a modification of Gerota's prussian blue-ether-turpentine mass. This was made by thinning 1 Gm. of artist's prussian blue oil paint with 4 cc. of turpentine, chemically pure, and diluting with 15 cc. of ether. This mass, when injected, immediately and easily filled the entire arterial and venous trees including the blood capillaries. The blue could be traced through the arteries and out the veins on the right and left sides. The entire specimen, which included the right and left thyroid glands, the right and left superior cervical lymphatic glands, the mediastinal lymphatic glands and all the extra-glandular lymphatic trunks departing from the thyroid, was fixed with the intervening and supporting connective in one large block (figs. 1 and 2). This was accomplished by pinning the specimen on a large sheet of cork and fixing it in a diluted solution of formaldehyde, U. S. P. (1:10) for over seventy-two hours. This entire specimen was then dehydrated and cleared according to the method of Spalteholz and preserved in methyl salicylate. The specimen as a whole was thus studied under the binocular microscope, following which free hand sections were made with a safety razor blade. These were cut from 0.5 to 5 mm. in thickness. Later, a portion of the right thyroid was run back through the alcohols and mounted in celloidin. From this block, serial sections were cut 10, 20, 30, 40 and 60 microns in thickness. These were stained in hematoxylin and eosin, and also in alum cochineal. The sections were studied under the binocular dissecting, as well as the compound, microscope.

Injections of the left thyroid were then carried out without previous ligation of the draining trunks. Three more successful injections of the right thyroid were obtained by injecting the 10 per cent solution of india ink directly into the left gland. In each of these animals the blood vascular system was injected primarily and the lymphatic vessels secondarily. This was accomplished by injecting the entire circulation of the head with the modification of Gerota's mass and in one the external carotid arteries with mercury. In the latter animal, Gerota's modified mass was also used, as the mercury could not be forced into the very small arterioles. The blue mass flowed by the mercury and filled the finest ramifications of the blood capillaries. Thus in four of forty dogs the narrow communicating plexus of lymphatic vessels was present between the right and left thyroid glands, and enabled one to inject only the lymphatic vessels of the right thyroid by inserting the mass into the parenchyma of the left thyroid. The presence of the pretracheal lymphatic reticulum may be more common than was revealed in this series of forty dogs in which it was discovered only four times. That the pressure of the injection of the india ink was more than sufficient for a complete injection of the right thyroid was proved by the presence of small extravasations

here and there in the pretracheal plexus (figs. 1 and 2). Direct extravasation of the ink into tissue spaces in the left thyroid into which the injecting needle was plunged could be ignored, because these extravasations were confined to the capsule of the left gland which was never used in this study. If ink happened to get into the blood capillaries, it would have been washed out through the veins in the first animal, because the dog was alive during the injection. In the remaining three the blood vascular tree was already injected, the veins then tied off and

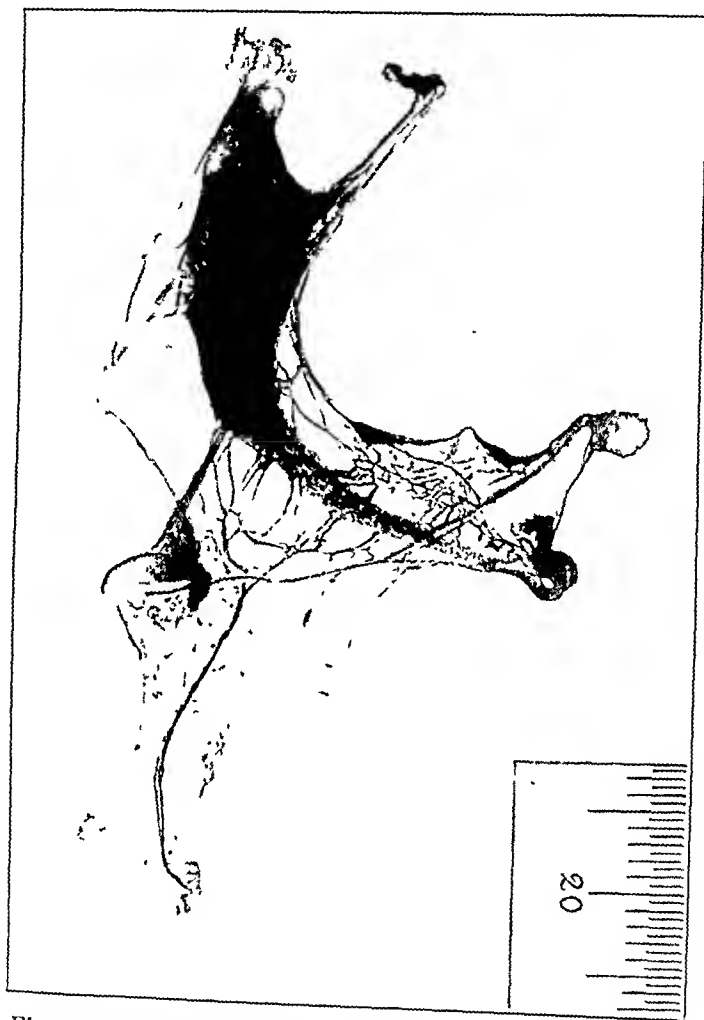


Fig. 3.—Photograph of an injected right thyroid gland with pretracheal fascia of dog 28; $\times 0.9$. Injection was made in a similar manner to that in dog 21. Note the pretracheal plexus with the efferent trunks draining into the mediastinal glands coursing through the pretracheal fascia. The lymphatics were injected with a 10 per cent solution of india ink and the blood vessels with a modified solution of Gerota's prussian blue.

the tension of the injection increased. Portions of the right thyroid of these later specimens were cleared by the Spalteholz method; some were mounted and cut in serial sections, while others were studied by maceration in 50 per cent hydrochloric acid and dissected under the binocular dissecting microscope. The intraglandular pattern having been determined for the dog, the human thyroid and that of the guinea-pig and the cat were studied in a similar manner. The superior

thyroid artery was first injected with the modified Gerota's injection mass. The lymphatic vessels were then injected by thrusting the needle directly into the lobe of thyroid to be studied. After the blood vessels were injected they could then be distinguished from the lymphatics. Although occasional extravasations occurred into tissue spaces, the knowledge of the interfollicular lymphatic pattern in the thyroid of the dog, together with the characteristic size and shape of the lymphatic channels in the human gland, left no doubt as to the similarity between the lymphatic system of the thyroid glands of dog and man.



Fig. 4.—Higher magnification of the pretracheal plexus of figure 2. This demonstrates more clearly the pattern of the lymphatic plexus and the shape of the lymphatic vessels through which the injection mass coursed to reach the right thyroid gland.

DESCRIPTION OF LYMPHATICS

The lymphatics of the thyroid originate in an anastomosing endothelial reticulum or plexus which lies in the interfollicular spaces of the gland (figs. 5, 6, 7 and 8). This interfollicular plexus consists of communicating capillary lymphatic channels which connect rather dilated endothelial sacs or small pockets that have been termed bursellae¹⁰

10. Bursa from βύρσα, meaning a leathern bottle; Latin feminine noun, bursa; bursella, diminutive of bursa; plural, bursellae.

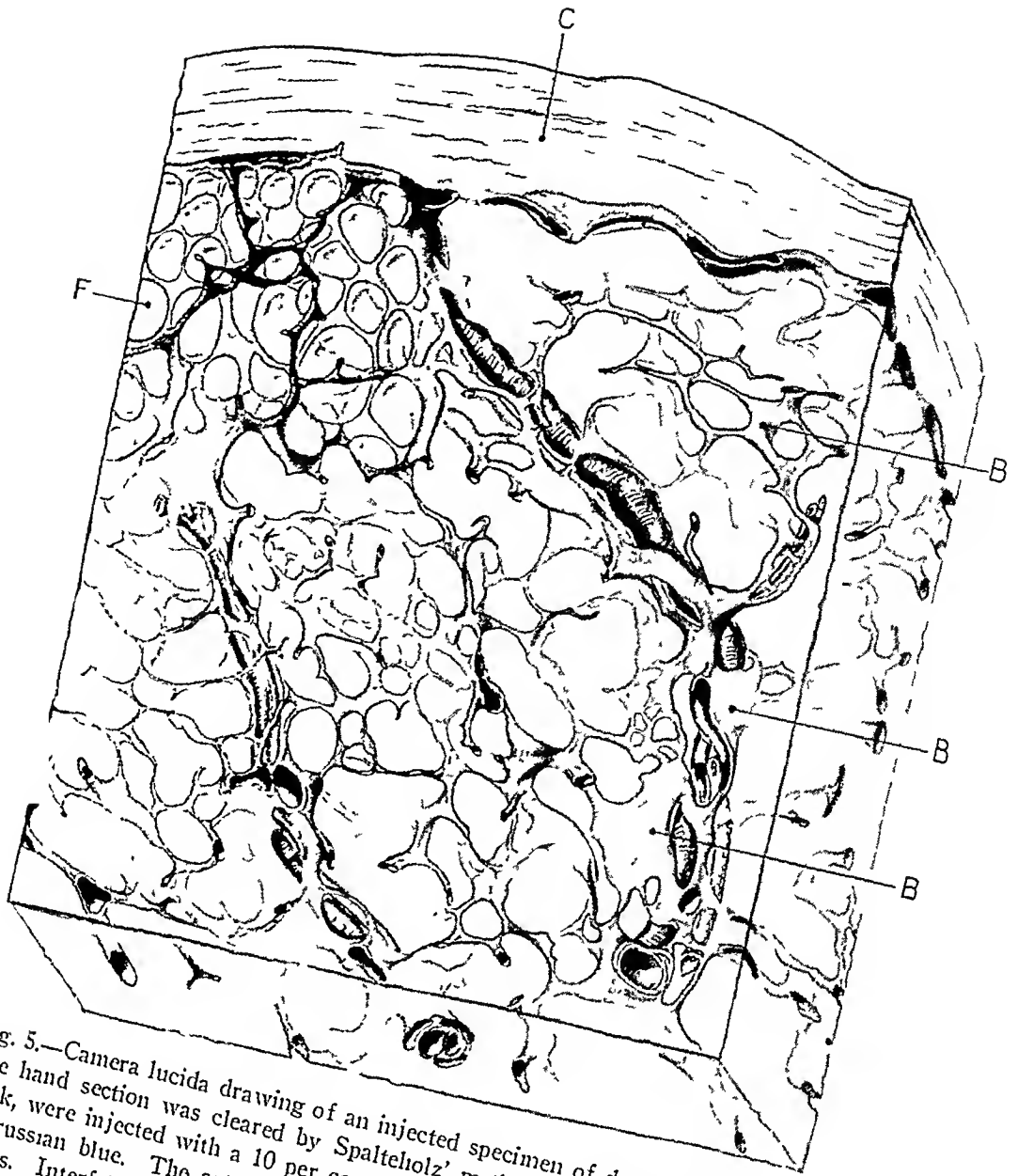


Fig. 5.—Camera lucida drawing of an injected specimen of dog's thyroid; $\times 57$. A free hand section was cleared by Spalteholz' method. The lymphatics, shown in black, were injected with a 10 per cent solution of india ink; the blood vessels, with prussian blue. The artery is colored pink in the drawing for the sake of clearness. Interfollicular lymphatic plexus consisting of lymphatic capillaries and bursellae is shown alone and also in relation to the blood vessels and follicles. In the upper left hand corner of the drawing, the individual follicles are drawn in their relation to the interfollicular lymphatic plexus. A higher powered drawing of this isolated area is shown in figure 6. In this region also the type of communication between the interfollicular lymphatic plexus with the overlying extraglandular plexus may be seen. Relatively large lymphatic capillaries run directly into the bursellae and also into the large spaces in the extraglandular plexus. It is to be noted also that the lymphatic plexus on the surface of the gland is beneath the capsule and contiguous with the underlying follicular parenchyma of the thyroid. The manner in which the lymphatic vessels surround the blood vessels is also to be noted, for it will be seen in the lower portion of this figure that the vein and artery are apparently surrounded by a lymphatic space, that is if only the cut end of the vessel is seen, but it will be noted that this is really an illusion because it just so happens that the vessel was cut across at a point in which one of the bursellae and its joining lymph capillary encircled the vein. The perivascular lymphatic network is abundant. The details of the blood capillary plexus have been omitted from this drawing in order to depict the lymphatic vessels more clearly. The relation of the lymphatic and blood capillaries together with the individual follicles of the thyroid may be seen in figure 6. Taking the lymphatic pattern as a whole, the alveolar arrangement formed by the rather large coarse lymphatic vessels is apparent. C indicates capsule; B, bursellae and F, follicle.

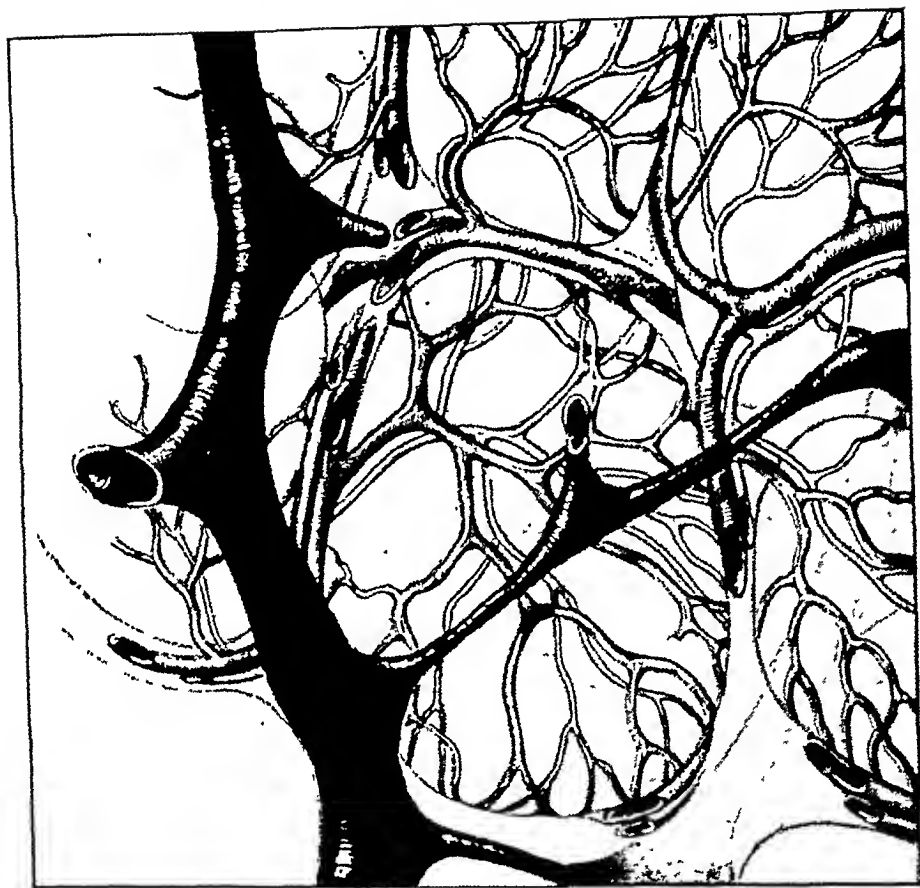


Fig. 6.—Enlarged drawing of the region shown in the upper left hand corner of figure 5, demonstrating the relative size and relation of the lymphatic and blood capillary plexuses to the individual follicles. It is to be noted that the lymphatic plexus lies external and less intimately in contact with the individual follicles of the gland. The blood capillary plexus is specific for each follicle, which is not true of the lymphatic capillary plexuses.

(figs. 5 and 6). These bursellae, together with the connecting lymphatic capillaries, form a closed lymphatic system. The bursellae are small dilated endothelial spaces or lacunae which lie between groups of follicles and from which emanate the connecting lymphatic capillaries. They vary in size from a slight knoblike enlargement occurring at the junction of two or more lymphatic capillaries to that of a broad, sheet-like structure which partly embraces a group of follicles or some of the larger arterioles (fig. 5). They are of an average size which is fairly regularly maintained throughout the thyroid and seems to be determined by the number of connecting lymphatic capillaries. There is also a marked difference in the form of the bursellae, which varies from that of a ribbon shape to that of either a multifaced prism or a wide and flat sheet like structure (fig. 5). The bursellae are situated exterior to the blood capillary plexus, which surrounds each follicle, but conform to the curvature of the convex external surface of the follicles between which they lie (figs. 5 and 6). Depending on the size of the bursellae, the surrounding pressure probably determines their shape to a great extent. Thus a very small bursella may partially encompass only the external contour of less than one half of one follicle, whereas one of prismatic form, either triangular, pentagonal or octagonal, may impinge on several follicles with the greater portion of its facets (fig. 5). On the other hand, a bursella may present the form of a wedgelike endothelial sac which fits in between the space remaining among the follicles where the circumference of these spherical bodies do not impinge on one another. Finally, the bursellae may occur as a large endothelial sheetlike structure which partially embraces in its concave surface, an entire group of follicles including their capillary plexuses, only a portion of a sphere however being formed by a bursella. A group of follicles completely surrounded by endothelium was not observed. In minute detail the bursellae vary markedly in size as well as in shape and are individual, but generally their form is quite similar. Their distribution through the gland is fairly regular and numerous with their long axes approximately parallel to each other and to the greater diameter of the gland. The bursellae, together with their connecting lymphatic capillaries, when injected, appear in a thin section of a cleared tissue to have an alveolar-like arrangement (figs. 5, 7 and 8). In the interfollicular plexus, the bursellae are mainly connected by rather long unbranching lymphatic capillaries, but not infrequently they anastomose with each other by a rather wide connecting ribbon-like endothelial channel which appears to form practically a fusion between the bursellae. This is particularly noticeable along the blood vessels (figs 5, 7 and 8). The perivascular bursellae frequently appear as broad ribbon-like or band-like channels forming a narrow meshwork with small interstices about the blood vessel so that when cross-sections are made through

the mesh the entire blood vessel seems to be surrounded by a lymphatic channel (fig. 5). That this is only apparent, however, is shown by the serial sections. The perivascular reticulum may, however, consist of merely a network of lymphatic capillaries, the diameters of which are relatively the same and form a more delicate network than that formed by the bursellae. The smaller branches and tributaries of the arterioles and vessels are not as a rule embraced by the lymphatic vessels. At frequent intervals along the course of the blood vessels communicating

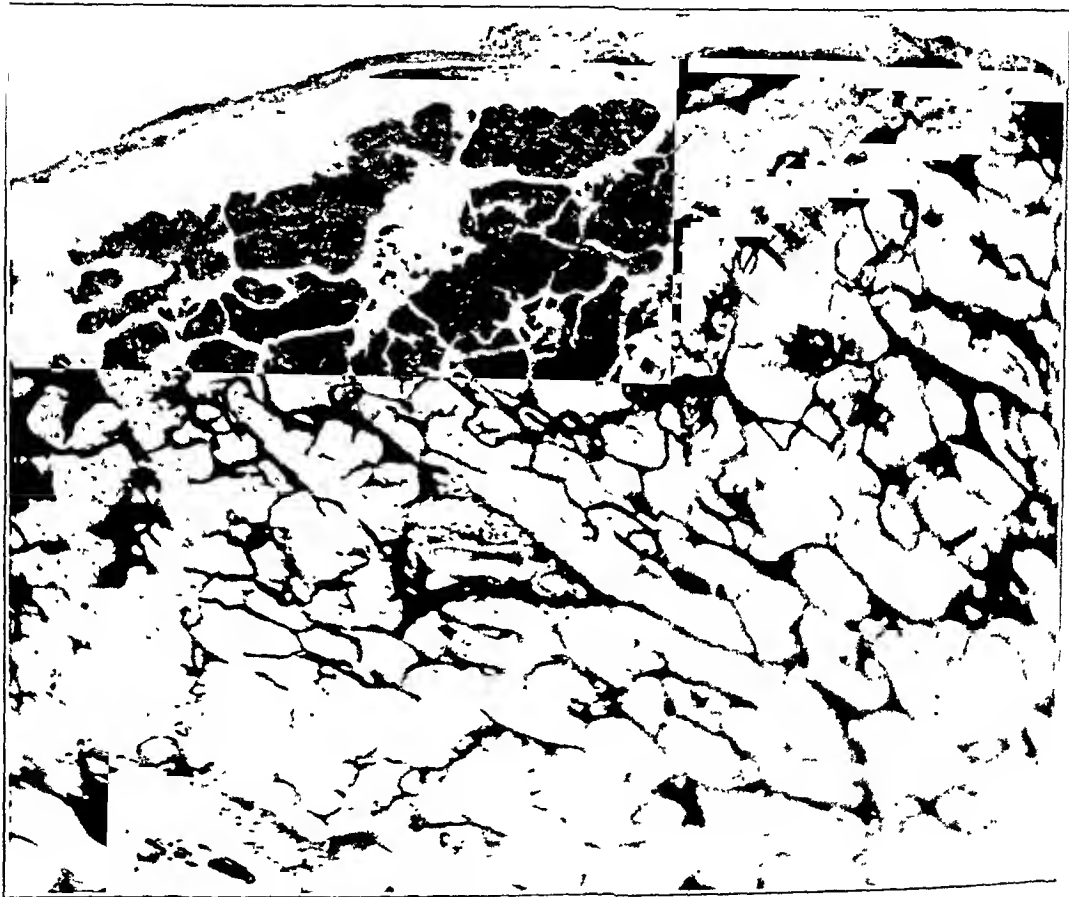


Fig. 7.—Photograph of an injected specimen of a dog's thyroid; $\times 4$. A free hand section was cleared with Spalteholz' method. A black perivascular interfollicular lymphatic plexus is shown connecting with the extraglandular reticulum. The dull gray background with white spots represents the capillary injection about the follicles. The capillaries were injected with prussian blue. Note the bursellae and lymphatic capillaries.

lymphatic capillaries from the interfollicular plexus anastomose with the perivascular reticulum. The lymphatic capillaries that form the channels of communication between the bursellae in the interfollicular plexus are characterized chiefly by their large size, both in length and diameter in comparison with the blood capillaries, by their infrequent

branching or reception of tributaries and by their lack of formation of a vascular network about individual follicles similar to the blood capillary plexuses (figs. 5, 6, 7 and 8). Occasionally the lymphatic capillaries would be arranged circumferentially about a group of follicles receiving radially arranged tributaries from a central nodal point or bursella. In one plane this disposition of lymphatic vessels had the appearance of an irregular wheel, but, as shown in the dissection of the macerated specimens, the rimlike peripheral lymphatic capillary also received tribu-

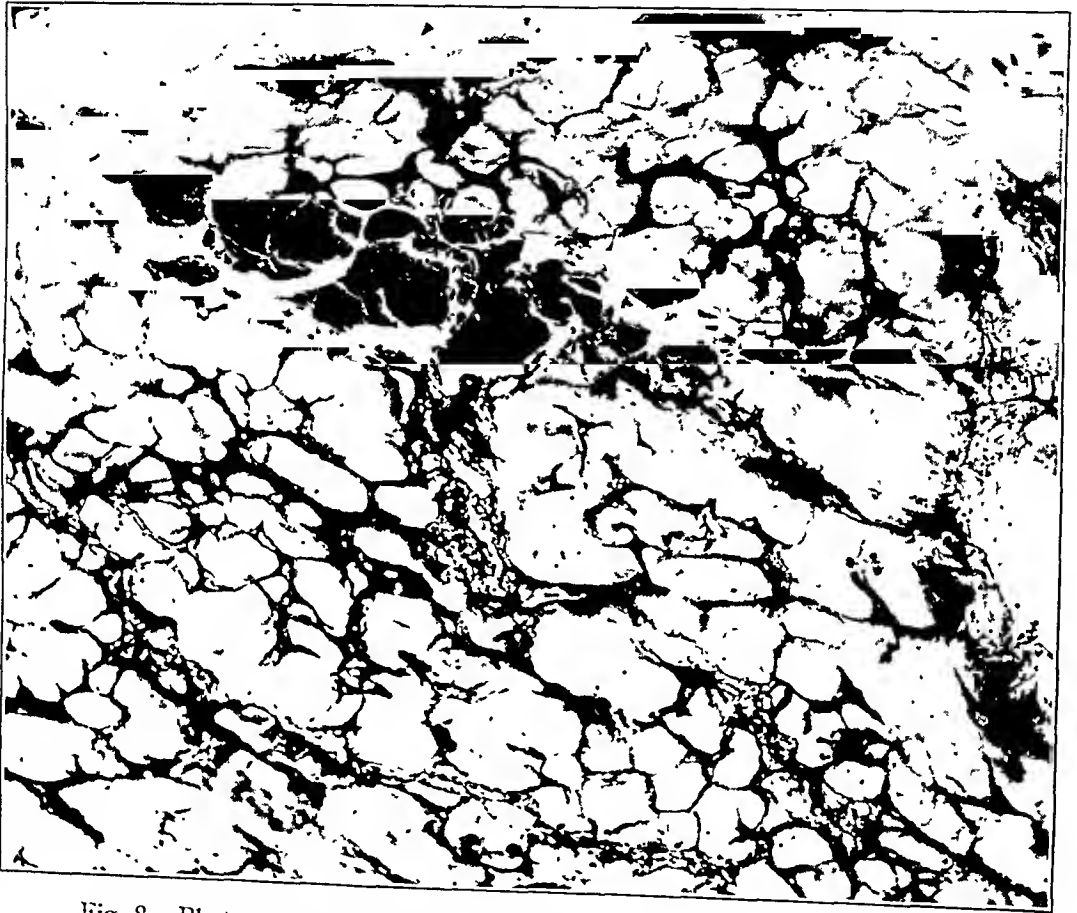


Fig. 8.—Photograph of an injected specimen of a dog's thyroid; $\times 4$. A sub-capsular lymphatic plexus is seen at the top of the figure. The lymphatics were injected with india ink. The alveolar nature of the interfollicular lymphatic plexus is shown. The very clear areas are groups of follicles surrounded by lymphatics. A free hand section was cleared by Spalteholz' method.

aries running in a plane perpendicular to it so that viewed in three dimensions the lymphatic capillaries formed a basket-like enclosure of a limited area of parenchyma. The lymphatic capillaries as shown in figures 5 and 6 are much more coarse and bulky in structure than the blood capillaries and appear to be less refined circulatory channels in which the flow of fluid is but one way, namely, away from the

parenchyma. In comparison, the blood plexus, consisting of arteriole, capillary and venule is uniform throughout for each individual follicle and consists of a finer and more delicate network of vessels through which the flow is in two directions (figs. 9 and 10). The great majority of the lymphatic capillaries are in direct continuity with the bursellae but a few begin as blind ends of cecal-like pouches which rest among the follicles external to the follicular blood capillary plexus. These blind end lymphatic capillaries, like the bursellae, probably represent the absorbing units of the interfollicular plexus. The entire interfollicular lymphatic capillary network with the bursellae lies, with reference to the follicle, external to the blood capillary plexus and unlike the latter does not



Fig. 9.—Photograph of a human thyroid follicle with an injected blood capillary plexus showing the intimate relation of the blood capillaries to the individual follicle; $\times 85$. This follicle with the blood capillary plexus was dissected from the normal human thyroid gland under the binocular microscope after fixation of the gland in a diluted solution of formaldehyde, U. S. P. (1:10) and maceration in a 50 per cent solution of hydrochloric acid at 60 C.

completely and specifically embrace each individual follicle. Thus the lymphatic vessels do not come intimately in contact with the follicles as do the blood vessels but seem to be absorbing units for larger regions of parenchyma or groups of follicles. Differing thus from the blood capillary system, the lymphatic capillary system is not individually devoted to separate and distinct follicles but rather to the spaces between groups of follicles or regions of parenchyma which require a drainage system for the carrying away of tissue fluids, probably not the internal secretion of the parenchyma. The latter, purely from an anatomical point of view, would be more likely to enter the blood stream due to the fact

that a specific vascular network surrounds each individual follicle, and the epithelial cells rest directly on a blood vascular reticulum. The specific secretion of the thyroid follicle would therefore have to go out of its way to avoid the more delicate blood capillary plexus to gain access to the lymphatic capillary plexus. This would seem unlikely from the structure alone, but, of course, is possible.

Serial sections were studied in order to determine the presence of any particles of ink either in the lumen of the follicles or within any so-called microlymphatic capillaries between the epithelial cells. However, in no instance in the 10, 20, 30 or 40 micron serial sections could there be demonstrated any communication between the lymphatic capillaries of



Fig. 10.—A photograph of the opposite side of the follicle shown in figure 9. This is merely to show the follicle is completely encompassed by a very abundant capillary network.

the interfollicular plexus described and the lumina of the follicles. The particles of ink were never observed to have entered the lumina of the follicles or to have penetrated between the epithelial cells. As observed in the cleared sections, the lymphatic capillaries were always situated externally to the blood capillary plexus which specifically embraced each follicle. A microcapillary lymphatic reticulum internal to the blood capillaries and coursing between the epithelial cells composing the follicles could not be demonstrated.

The remaining lymphatic vessels of the thyroid may be divided into two main plexuses: (1) an intraglandular plexus, which is composed of large collecting trunks situated on the surface of the parenchyma along

the course of the septums, and which form frequent anastomoses with each other and the interfollicular plexus (fig. 11); (2) an extraglandular plexus located about the outer surface of the thyroid external to the blood vascular network, which supplies the gland, but beneath or internal to the fibrous capsule investing the thyroid (fig. 12). From the latter plexus originate the larger collecting trunks that accompany the superior thyroid vessels to the cervical lymph glands and also the trunks that form a reticulum in the pretracheal fascia draining into the medi-



Fig. 11.—Photograph of an injected specimen of thyroid of a dog, showing the intraglandular plexus along the course of one of the septums dividing the parenchyma of the thyroid gland; \times 12. In the middle of the figure is a large, dense black trunk showing a blood vessel partially injected with mercury. To the right of this dense trunk can be seen the beginning of the efferent lymphatic trunks and their formation from the surface plexus, X. In the upper left hand corner is a parathyroid gland, the lymphatics of which were not injected and evidently not in communication with the lymphatics of the thyroid.

astinal glands (figs. 1, 2, 10 and 11). Except for an increase in size, the interfollicular, intraglandular and extraglandular lymphatic system of the human thyroid is identical with that of the gland in the dog.

COMMENT

From a review of the previous contributions to the study of the intraglandular lymphatic plexus of the thyroid, one is forced to the conclusion that the method of direct puncture of a parenchymatous organ results in the injection of not only lymphatic vessels but also tissue

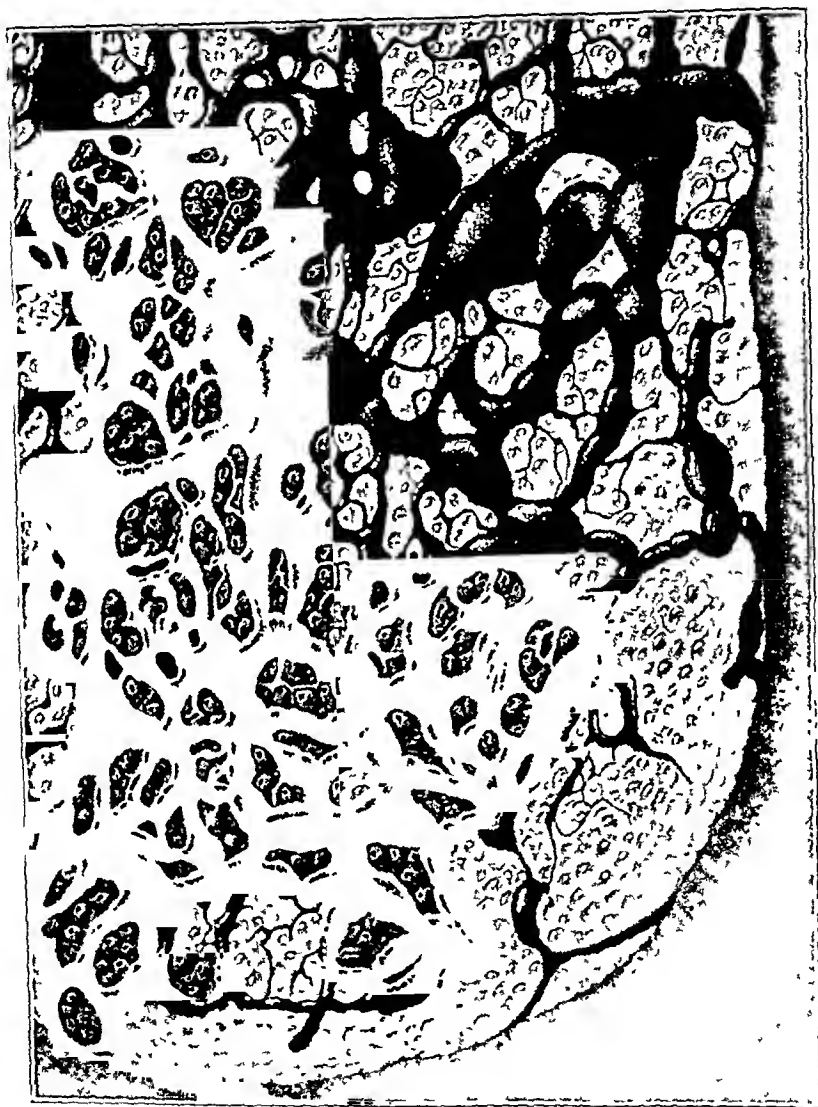


Fig. 12.—Camera lucida drawing of the surface or the extraglandular plexus of a dog's thyroid showing individual follicles of thyroid and the communications from the interfollicular plexus running into the large lacunae of the surface plexus; $\times 15.5$.

spaces and blood capillaries. This unsatisfactory method of injection resulted in many controversial reports and discussions in the literature which have persisted until the present time in a rather periodic manner as interest in the subject waxes and wanes, throughout the years. It

appeared that this problem was insoluble, until by good fortune four dogs were encountered which happened to be anatomically so designed as to afford a lymphatic plexus across the midline from one thyroid body to the other. Thus for the first time it was possible to inject completely only the lymphatic vessels of the thyroid gland and be certain that only the lymph channels had been injected. The narrow anastomotic lymphatic



Fig. 13.—Photograph of the efferent trunks, *b*, draining the superior pole of the right thyroid, *d*, into the superior cervical lymph gland, *a*. *C* is the superior thyroid artery; $\times 2.1$.

plexus joining the two thyroids in the dog is inconstant and would seem to be present in about 10 per cent of the animals. This plexus cannot therefore be considered a normal drainage pathway, nor can it be thought of as a route of collateral circulation, for it has never been shown that the latter develops in the lymphatic system. The fact remains that since

this plexus is not one which functions as a series of efferent drainage lymphatic vessels, fluid injected into these vessels would flow unobstructed by valves into only the normal lymphatic channels of the gland. Therefore, by the maintenance of a constant head of pressure, complete injection of the finest ramifications of the lymphatic capillaries could

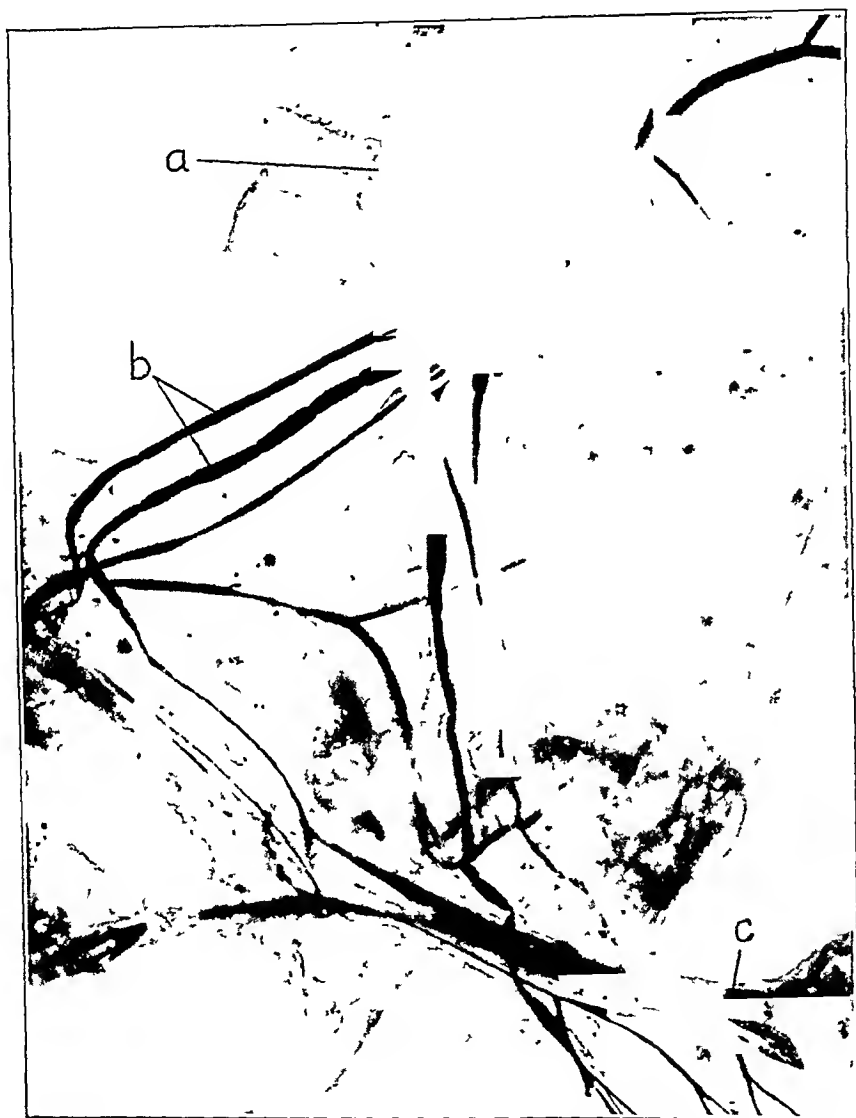


Fig. 14.—Photograph of the same specimen as shown in figure 13; $\times 3.6$. The lymphatic trunk is shown draining into the superior cervical lymph gland. *a* is the superior cervical lymph gland; *b*, the efferent lymphatic trunks of the superior pole, and *c*, the superior thyroid artery.

be accomplished. The progression of the india ink within the thyroid also spoke for the completeness of the injection. Only a portion of the surface of the lower pole contiguous with the pretracheal plexus became filled with the solution of india ink, then the center of the thyroid became

injected, following which the surface lymphatic vessels and their drainage trunks were in turn filled with ink. Apparently only certain regions of the interfollicular plexus are drained by specific trunks of the intraglandular and extraglandular lymphatic vessels, and these in turn supply specific efferent trunks which join with similar large channels away from the gland. Therefore, to enter these different channels of the intraglandular and extraglandular plexuses, the solution injected must completely fill the interfollicular network under sufficient pressure to force the solution out along various routes of drainage. The incidence of occasional slight extravasations in the specimens proved the presence of sufficient pressure within the lymphatic capillaries. The fact that the right thyroid gland was jet black with the solution of ink that had filled the entire lymphatic system inside and outside of the thyroid, including the superior cervical and mediastinal lymphatic glands, and the fact that the long unbranching lymphatic capillaries composing the interfollicular plexus were bulging with the solution are evidence of the completeness of the injection. If any smaller capillaries had been present, they would have become filled or at least partially filled in some regions and in some instances. Thus it is felt that complete injection has been accomplished only of the lymphatic system. The simultaneous injection of the blood and lymphatic vessels with different colored masses, the former blue and the latter black, brought out in marked contrast the striking difference in the relation of these two systems to the individual follicles.

The blood capillaries form a complete network about each follicle with the epithelial cells resting directly on the endothelial wall of the capillary (figs. 9 and 10). The blood capillaries in general run parallel to each other from the vessel of ingress to that of egress. The lymphatic capillaries form a much more coarse and less intimate plexus in regard to the follicles, being situated entirely outside of the blood capillary plexus. Individual follicles were nowhere observed to be served with a specific lymphatic reticulum or in direct contact with either the lymphatic capillaries or bursellae. The lymphatic plexus occupied the intervals between the parenchymatous elements and, from the apparent structure of this system, would serve to drain off the accumulation of nonspecific tissue juices. In certain regions of the cleared sections and also in the serial sections, one or more follicles would lie in the concavity of a bursella, but the blood capillary plexus always lay internal to the lymphatic vessels, and in no instance could any follicles be found that were completely surrounded by one or more bursellae.

The intracellular and intercellular ducts described by Matsumaga were probably artefacts resulting from extravasations into tissue spaces

about the follicle. It is possible by injecting directly into the parenchyma of the gland to be studied, as Matsunaga did, to force the injection mass into channels other than the lymphatic vessels. Again, and that which seems more likely, is that Matsunaga mistook the thickenings or condensations of the intercellular cement substance, called terminal bars that surround epithelial cells in a vast interlacing network, for microcapillaries of the lymphatic system. Wilson¹¹ recently showed that the "tubules" or "microcapillaries" of secreting epithelium are terminal bars which do not appear at all times, and which often appear only in localized areas of a tissue. For a complete discussion of the subject of microcapillaries, one should refer to Wilson's admirable contribution. Frey, Boechat, Navalichin and Baber undoubtedly injected successfully the interfollicular lymphatic channels, but unfortunately the tissue spaces as well, which made their conclusion in part erroneous. Williamson and Pearse concluded that the lymphatic system in the thyroid was an open one, without having made injections into the gland. In this study the lymphatic system was found to be a closed one, as elsewhere in other regions and structures of the organism. The so-called "gland unit" described by Williamson and Pearse could not be demonstrated.

In the study of the human thyroid it is to be admitted that the conclusions arrived at are based to a great extent on analogy with the thyroid of the dog. However, in every instance in which an obviously good injection of the lymphatics was obtained in a region of the gland remote from the point of injection, the pattern of the interfollicular plexus was identical with that of the dog. It is to be recalled that the blood vascular system in man was previously injected with Gerota's prussian blue mass. The extravasations into tissue spaces occurring about the point of injection were easily recognized and impossible of confusion with the intraglandular lymphatic system, after one had become acquainted with that of the dog.

In order to be certain that the 10 per cent solution of india ink would penetrate the finest capillary bed, injections were made into the blood vascular system of the intestine and thyroid of the dog, with the result that the solution of ink permeated and completely filled the blood capillary branches.

The exact location at which absorption occurs in lymphatic vessels has not been determined, but if some speculation in this respect may be permitted from a purely anatomic point of view, the blind cecal-like capillaries and the bursellae appear to me to be the chief centers of this activity in the thyroid.

11. Wilson, Gale E.: The Nature of the So-Called Microcapillaries of the Thyroid Gland and Other Secreting Epithelia, *Anat. Rec.* **42**:243 (May 25) 1929.

SUMMARY

1. Complete injection of the lymphatic vessels of the thyroid gland of the dog has been accomplished by filling the lymphatic channels at a point remote from the gland.
2. A comparative study has been made of the human thyroid as well as of the thyroid of the guinea-pig and of the cat.
3. The lymphatic system of the thyroid is a closed one.
4. It would seem unlikely, from a purely structural standpoint, that the specific secretion of the gland is transmitted by this system.

PRIMARY CARCINOMA OF THE JEJUNUM

REPORT OF A CASE *

FRANKLIN I. HARRIS, M.D.

Associate Chief Surgeon of Mount Zion Hospital

AND

HAROLD ROSENBLUM, M.D.

Intern, Mount Zion Hospital

SAN FRANCISCO

Primary carcinoma of the jejunum is of interest because of its rarity, because of its amenability to proper surgical treatment and because of its disturbing tendency to be overlooked in diagnosis. The jejunum is relatively highly immune to the development of primary carcinoma, more so than any other portion of the intestine, including the duodenum.

Accurate estimation of the percentage of the occurrence of primary carcinoma of the jejunum is difficult because of its rarity, but a review of a large series of autopsies reveals that the incidence of this condition is roughly 1 per cent of all intestinal carcinoma.

REVIEW OF THE LITERATURE

A series of 41,883 autopsies at the Vienna General Hospital (Johnson¹), including 343 cases of intestinal carcinoma, did not reveal a single case of carcinoma of the jejunum.

In 1904, Notlmagel² found 9 cases in 3,585 deaths from cancer. In 1927, Hellström³ collected from the literature 70 cases of carcinoma of the jejunum and ileum in which operation had been performed, and added 3 more. Since then cases of carcinoma of the jejunum have been reported by Morrison,⁴ Roblee⁵ and d'Allaines,⁶ who have each added a case.

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* From the Surgical Service of Mount Zion Hospital.

1. Johnson, R.: Carcinoma of the Jejunum and Ileum, *Brit. J. Surg.* **9**:422, 1922.

2. Notlmagel, H.: Gould and Pyle's *Cyclopedia of Practical Medicine and Surgery*, Philadelphia, P. Blakiston's Son & Co., 1904, vol. 8, p. 428.

3. Hellström, J.: Primary Cancer in Jejunum and Ileum, *Acta chir. Scandinav.* **62**:465, 1927.

4. Morrison, W. R.: High Intestinal Obstruction Caused by Primary Carcinoma of the Proximal Jejunum, *Am. J. Surg.* **2**:154, 1927.

5. Roblee, M. A.: Secondary Adenocarcinoma of the Ovaries from the Jejunum, *Am. J. Obst. & Gynec.* **18**:790, 1929.

6. d'Allaines, F.: Sur l'épithélioma primitif du jejuno-iléon, *J. de chir.* **33**:449, 1929.

Primary carcinoma of the jejunum occurs in persons relatively younger than those in whom carcinoma develops elsewhere in the intestines. The decade of greatest incidence⁶ is from 30 to 40, and men are affected about twice as often as women.³

Type of Lesion.—The type of lesion observed on gross examination is most often a circular, constricting, scarred tumor. Less frequently, the growth is ulcerative and nonconstricting. Histologically, the growth is nearly always adenocarcinomatous, frequently exhibiting a marked desmoplastic reaction. Colloid carcinoma of the jejunum occurs rarely.⁷ Primary carcinoma may be simulated by secondary melanopithelioma and by secondary adenocarcinoma of the ovary and the uterus. Primary carcinoma of the jejunum metastasizes relatively late to the regional retroperitoneal lymph nodes. Roblee⁵ showed that carcinoma of the jejunum can metastasize to the ovaries; this fact should be borne in mind in diagnosing and treating the latter condition.

Symptoms.—The symptoms of carcinoma of the jejunum depend on whether or not the growth obstructs the intestinal lumen. The stenotic type, which is the commoner, causes epigastric distress and cramps, constipation and diarrhea, vomiting of large amounts of fluid (frequently bile-stained⁸) and, occasionally, visible peristalsis. There is no distention, fecal vomiting or palpable tumor. The nonstenotic type, rarer and more insidious, causes anemia due to hemorrhage—which is nearly always present and which may simulate pernicious anemia (Denck⁹)—easy fatigability and, during the later course of the disease, emaciation. Anemia may be the only sign.

Diagnosis.—Carcinoma of the jejunum should be considered in the presence of colic in the upper portion of the abdominal midline with vomiting, particularly if the vomitus is bile-stained. Pyloric stenosis may be closely simulated. The presence of blood in the stools, otherwise unaccounted for, is important and suggestive. Roentgen examination shows delayed emptying of the stomach, dilatation and atony or stenotic peristalsis in the occluding type and sometimes a frank defect in outline. Gastric analysis shows a low amount of absence of hydrochloric acid due to the regurgitation of bile.¹⁰

Treatment.—The treatment for jejunal carcinoma is surgical. The operation may be radical or palliative, i. e., resection or gastro-enterostomy may be employed, the latter to give relief from obstructions.

7. Craig, W. McK.: Lymph Glands in Carcinoma of the Small Intestines, Surg., Gynec. & Obst. **38**:479, 1924.

8. Cade, A., and Devic, A.: Cancer d l'angle duodenojejunal. Arch. d. mal. de l'app. digestif **10**:419, 1920.

9. Denck, G.: Zentralbl. f. Chir. **54**:154, 1927.

10. Lundberg, S.: Carcinoma of the Duodenojejunal Flexure. Acta chir. Scandinav. **56**:417, 1924.

Radical treatment by resection resulted in a mortality of 38 per cent in 26 cases (Venot et Parcelier¹¹) and 36 per cent in 70 cases (Hellström⁵). The immediate mortality, however, was 70 per cent in those cases in which operation was performed during acute obstruction and only 18 per cent in those cases in which operation was done when no acute obstruction was present. The primary mortality in 23 cases of palliative operation (gastro-enterostomy) was 43 per cent, while the primary mortality in a series of 23 cases in which radical operation was performed was 36 per cent. Radical operation is considered the method of choice, because (1) regional lymph nodes appearing at the operating table to be carcinomatous are frequently only inflammatory; (2) the spread of the growth is essentially slow; (3) the immediate mortality has been shown to be no greater, and (4) removal of the primary focus may cause a retardation or retrogression of metastases.

Prognosis.—Radical operation offers a 16 per cent chance of cure. Since the growth spreads slowly and is comparatively easily removed in early, uncomplicated cases, earlier diagnosis would improve this percentage. The nonoccluding type of carcinoma offers a poorer outlook because of its insidious manner of growth.

REPORT OF A CASE

History.—Mrs. B. W., a white woman, aged 42, an American housewife, entered the hospital on Feb. 24, 1930. She presented weakness, pallor, shortness of breath and pain in the back. Her mother had died at the age of 54 of "obstruction of the bowel;" otherwise the familial history was irrelevant.

Three years previous to admission, curettement had been done. This was followed by left salpingo-oophorectomy and appendectomy. The eyes, ears, nose, mouth and throat were normal. Constipation had been present for several years. The genito-urinary tract had been normal. Menstruation began when the patient was 15. Menorrhagia and dysmenorrhea had always been present. Nine years previously, the patient began having odorous, black, vaginal discharges following each period and lasting almost until the next. Relief was given by the operation previously noted. The patient was married at the age of 34; there had been no pregnancies. The average weight of the patient was 128 pounds (58.1 Kg.). The weight on admission to the hospital was 115 pounds (52.1 Kg.); one year previously it was 122 pounds (55.3 Kg.). Her habits were good.

About two and one half years previous to admission, the patient noticed weakness, pallor and nervousness, which gradually increased. Later the patient consulted a doctor, who said that she had pernicious anemia; she was treated with injections of iron and was given a liver diet. About that time she began to notice cramplike pains in the upper abdominal region; this condition was not relieved by food or sodium bicarbonate, and it was not associated with vomiting. She also noted increasing dyspnea on exertion and edema of the ankles. The aforementioned symptoms became progressively worse. The patient then began to note a numbness of the fingers and the toes and a dragging ache in the lumbar region. There was no history of vomiting, bloody or tarry stools, icteric or clay-

11. Venot et Parcelier: *Rev. de chir.* 47:678, 1913.

colored stools. The mouth and the tongue were sore. There were no urinary symptoms. On two occasions during the year and a half preceding her admission to the hospital, roentgen examinations of the gastro-intestinal tract did not show any pathologic condition.

Physical Examination.—The patient was a pale, emaciated, apprehensive woman of about 42; she complained of pain in the back. The skull and the scalp were normal. The skin and the mucous membrane were markedly pale. The eyes reacted normally to light and in accommodation, and the pupils were equal and regular. The nose, mouth and throat were normal. There was no glandular enlargement in the neck, and the thyroid gland was of normal size. Examination of the thorax gave negative results. The expansion of the lungs was full and equal; there was a vocal fremitus; percussion was resonant; auscultation gave negative results. The breasts were wasted; there were no masses. The heart showed the apex visible and palpable in the fourth interspace in the midclavicular line; the beat was forceful; the rate was 88; the rhythm was regular; the tones were loud and high pitched. There was a blowing systolic murmur at the pulmonary area transmitted down the left sternal border and toward the apex. The arteries of the peripheral vessels were not palpable. The blood pressure was 144 systolic and 70 diastolic. The abdomen was moderately distended. There was a scar in the lower portion of the abdominal midline extending from the umbilicus to the pubes. There was no tenderness; the liver and the spleen were not felt; masses were not palpable. Pelvic examination showed a contracted vaginal outlet. The uterus was atrophic and was fixed in the anterior position by adhesions. The fornices were normal. The cervix was atrophic, but otherwise healthy in appearance. Rectal and proctoscopic examinations gave negative results. There was slight edema of the feet and ankles. The reflexes were brisk. There were no pathologic reflexes, and there was no impairment of the sense of position or of vibration. Moderate diffuse tenderness was present in the region of the sacroiliac joints.

Laboratory Examination.—On February 24, examination of the blood showed: hemoglobin, 16 per cent; red blood cells, 970,000; white blood cells, 11,650; polymorphonuclears, 88; lymphocytes, 8; basophils, 1; transitionals, 3; reticulocytes, 2.5 per cent; platelets, 200,000; color index, 0.45; icteric index, 3; marked achromia and anisocytosis. Urinalysis gave negative results, except for a few pus cells. The urobilinogen was normal.

Examination of the stool gave negative results, except for occult blood, 3+. Examination of 20 cc. of the contents of the fasting stomach revealed: a colorless specimen, a normal amount of mucus and of rennin, no micro-organisms and absence of free hydrochloric acid. The tests for pepsin and for occult blood gave negative results.

An Ewald meal was given, and the first specimen, 10 cc. of the contents of the stomach, showed: a colorless specimen, a normal amount of mucus and of rennin, hydrochloric acidity 10, and total acidity 38. The test for pepsin gave negative results.

The bleeding time was one and one-half minutes, and the coagulation time, five minutes. The blood belonged to blood group no. 2 (Moss).

After the transfusion of 500 cc. of whole blood on February 25, the hemoglobin was 31 per cent and the red blood cells numbered 2,800,000.

February 28: Roentgen examination by Dr. Lloyd Bryan showed: lung fields, clear; heart and arch, normal; no delay in the esophagus; good tone, good position and free movement of the stomach; no defects in gastric outline; peristalsis.

moderate; antrum and pylorus, smooth; cap, large, and smooth in outline. There was considerable dilatation and delay in the descending and transverse duodenum. In the last portion of the duodenum there was a narrow constricted area directly beyond which there was a round smooth indentation about 2.5 cm. in diameter, which suggested a polyp or a benign tumor (fig. 1). A diagnosis of pancreatic tumor or some other type of retroperitoneal tumor, with pressure on the small bowel, could not be excluded. An opaque enema showed the colon to be normal.

March 3: After the transfusion of 500 cc. of whole blood, the hemoglobin was 53 and there were 4,100,000 red blood cells.



Fig 1.—Roentgenogram showing a polypoid-like irregularity in the first part of the jejunum. This mass proved to be carcinoma. The same radiographic picture was seen on plates taken six months previously, but no significance was attached to it at that time.

Preoperative Diagnosis.—(1) A polyp in the first portion of jejunum; (2) carcinoma of the body of the pancreas.

Operative Procedure.—March 4: An incision was made in the upper midline. When the peritoneal cavity was opened no free fluid was noted. The mesocolon was lifted back on the epigastrium, and the proximal portion of the jejunum was exposed. It was noted that in the region of Trite's ligament, the jejunum was absolutely fixed and seemed to extend from a large hard mass which appeared to

be retroperitoneal and to involve the entire surface of the pancreas. Digital exploration of the lumen of the fixed portion of the jejunum showed it to be constricted so that the latter could not be moved; it appeared to have a hard cartilaginous lining which was suggestive of annular malignancy within the bowel at the portion of the jejunum immediately distal to the duodenojejunal junction. No attempt was made to explore this mass further, as it seemed to be fixed and there was apparently a hemorrhagic infiltration into the free portion of the jejunum as it came out of the mass. A small gland was felt at the mouth of the mesentery of this proximal portion of the jejunum, and this was carefully excised and saved for microscopic examination.

In view of the fact that the duodenojejunal region apparently was doomed to absolute obstruction in the near future, it was decided to do a gastro-enterostomy. This was done in the usual manner. A little difficulty was encountered in going through the mesocolon, for it appeared to be closely adherent to the posterior wall of the stomach, possibly the result of an inflammatory reaction from the malignant process occupying part of the lower segment. There were also noted in the anterior region of the wall of the stomach two small, hard nodules, the size of a pinhead, which were suggestive of metastases. Exploration of the liver showed it to be apparently free from metastases, and no glands were felt in the mesocolon or the omentum. The abdominal incision was closed by heavy, braided silk.

The postoperative diagnosis was retroperitoneal tumor, possibly sarcoma; carcinoma of the pancreas.

Postoperative Course.—The patient's convalescence was satisfactory for the first five days following operation. On the sixth day after operation, symptoms developed that were suggestive of partial intestinal obstruction. These symptoms and signs were very indefinite, however, and continued with some remission until March 16, when the patient's condition took a sudden turn for the worse and operation was again performed. A complete intestinal obstruction was found due to knuckling of a loop of small bowel which was incarcerated in some old adhesive bands low down in the pelvis; this condition was the result of a laparotomy performed three years before. The patient was in extremely poor condition, and died the following day.

The following observations were made at autopsy by Dr. G. Y. Rusk, professor of pathology, University of California Medical School:

Overlying the spinal column behind the stomach and extending to about 5 cm. below the pancreas was a mass of tissue. This region was removed, together with the adjacent viscera. The stomach was of normal size. A gastrojejunostomy had been performed, the operative region being in excellent condition. The stomach readily admitted two fingers. The mucous membrane of the stomach, except for this opening, appeared to be normal. On continuing the opening of the intestinal tract at a point just beyond the duodenum there was found an extensive, ulcerated rough area with excrescences from granular to nodular and with apparently persistent mucous membrane scattered over a hyperemic surface. The ulcerated area encircled the intestine for a distance of about 7 cm. The wall of the intestine showed some slight thickening, but in general the condition appeared to extend superficially rather than to invade. At approximately the center of the ulcerated area, on its superior and posterior aspects, a channel occurred which admitted the little finger, and a mass of tissue extended upward and backward behind the pancreas and behind the stomach. This mass of tissue formed an irregular, broad

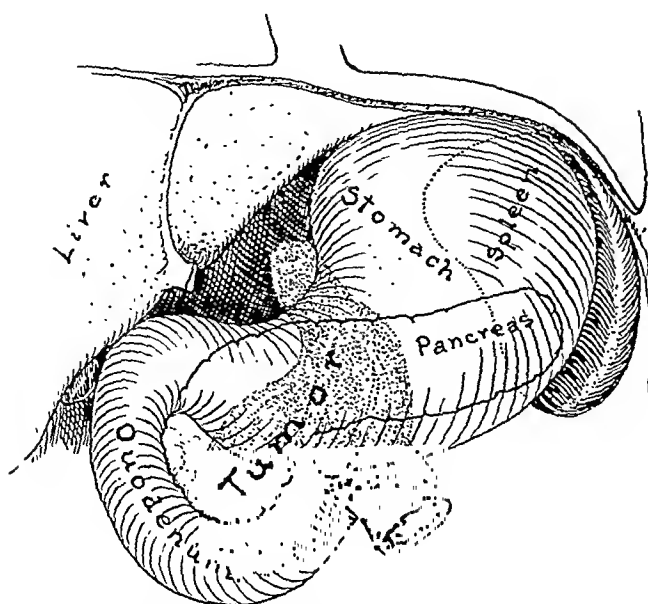


Fig. 2.—Diagrammatic sketch showing extent of tumorous mass arising from the primary carcinoma of the jejunum.

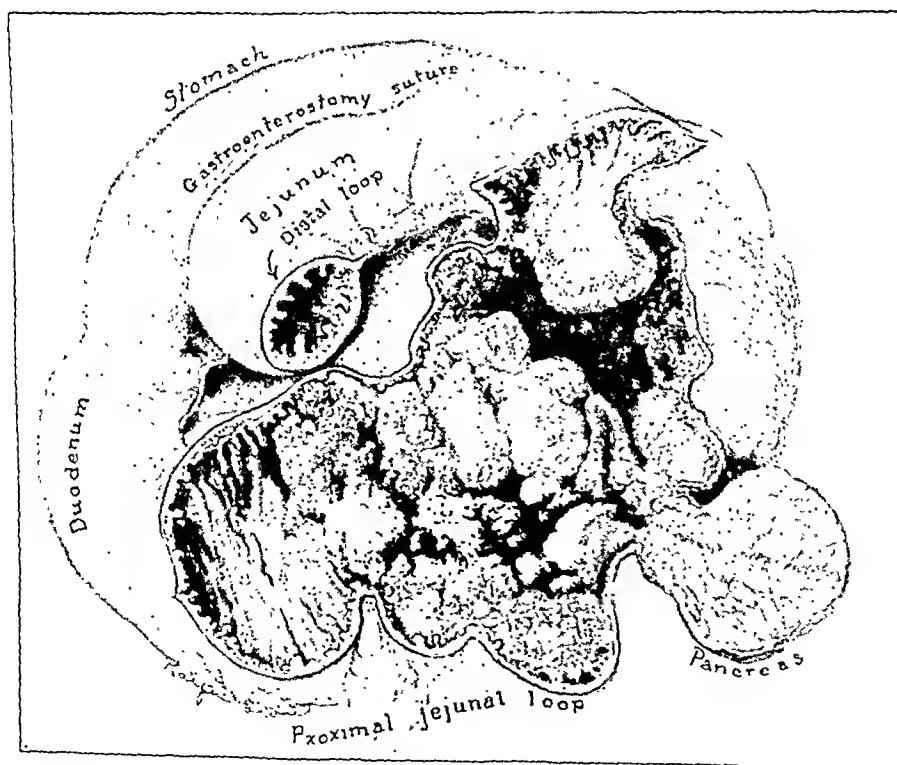


Fig. 3.—Drawing made from autopsy showing the primary papillary adenocarcinoma of the jejunum.

cord, externally fibrotic, but on section showing irregular patches of necrosis and at times fine stippling in a background of translucent connective tissue. The fibrotic reaction extended into the pancreas as it passed. There were adhesions in the lesser sac, and the upper portion of this mass formed a bulging area on the posterior wall of the stomach directly to the right of the midline. This bulging covered an ovoid area about 3 by 4 cm. No evidence of distant metastasis was found. Following the lumen of the jejunum, the gastrojejunostomy was again encountered.

The internal genitalia were matted in chronic adhesions, as previously noted. The uterus and the bladder appeared to be normal. The right ovary seemed small and showed superficial adhesions. The mesenteric lymph nodes appeared moderately enlarged, but were otherwise normal.

Under microscopic examination, sections of the carcinoma that were taken from the jejunum adjacent to the point of perforation showed a bit of mucous membrane with normal epithelium which ceased rather suddenly. Here the surface showed the same characteristics of the general carcinomatous process. The new growth abruptly broke through the submucosa and consisted of a more or less delicate branching stroma in the interstices of which there was a papillary adenocarcinomatous structure (fig. 3). The epithelial cells of the growth were of a fairly uniform type; they were cuboidal and were usually one layer thick; occasionally they formed small thickened clusters. In the stroma there was a moderate amount of lymphocytic infiltration in places, and two small thrombosed vessels were seen. Several sections taken from the depths showed extensive necrosis; groups of adenomatous and papillary structures were seen in the necrotic regions; there were also areas in which the carcinomatous tissue grew diffusely, and there was a more or less desmoplastic background. At the various levels, cells in mitotic division occurred, but they were not numerous.

The liver, pancreas, spleen, stomach and kidneys showed no evidence of metastatic involvement.

SUMMARY

In cases of primary carcinoma of the jejunum that have been reported, this growth is noted for its infrequency. The history of the present case illustrates the error which is frequently made, namely, the diagnosis of this condition as pernicious anemia. Roentgen examinations by a competent man may also give erroneous results, unless the clinician directs the roentgenologist's attention to a careful examination of the intestinal tract immediately beyond the stomach.

Insufficient importance is attached to the patient's complaint of pain in the lower portion of the back which is associated with severe anemia. This symptom should make one suspect the presence of a tumor in the region of the pancreas. The reference of pain from lesions in this locality is not generally known, and in cases of anemia it is often assumed to be due to the usual asthenia associated with both primary and secondary anemia.

Early diagnosis lends hope for radical resection with cure, as distant metastases are relatively infrequent. The case presented demonstrates an advanced growth which showed extension only into the immediate retroperitoneal region of the pancreas and the stomach, with no involvement of the adjacent mesenteric lymph nodes.

OSTEOGENIC SARCOMA OF THE LEFT TIBIA IN A PATIENT WITH OSTEITIS DEFORMANS*

PAUL J. BRESLICH, M.D.

The John Jay Borland Fellow in Medicine

CHICAGO

A review of the reports in the literature concerning the incidence of sarcoma in bones affected by osteitis deformans suggests that this complication may not be as common as the original work of Paget¹ indicated. Osteitis deformans is a comparatively rare disease, and in 1927, Bird² found that the incidence in the larger hospitals of Boston was only 1 in every 15,000 patients admitted. This agreed with the results reported by Da Costa, Funk, Bergeim and Hawk,³ who observed only 3 cases among 38,000 patients admitted to the Jefferson Hospital in Philadelphia. In 1901, Packard, Steele and Kirkbride⁴ collected 67 instances of osteitis deformans, of which 5, or about 7.5 per cent, were complicated by sarcoma of the bone. Higbee and Ellis⁵ stated that at least 5 of 158 instances of Paget's disease reported up to January, 1911, were associated with sarcoma of the bone, and Bird² in searching the records of four Boston hospitals found that among 64 patients with osteitis deformans 7 had sarcoma of the bone. Speiser⁶ stated that in 6 of approximately 150 cases of osteitis deformans that he collected in 1928 the bones had undergone sarcomatous degeneration. The incidence of sarcoma in Paget's disease has been estimated as high as 10 per cent, but according to Speiser⁶ it is about 2 per cent, since so many uncomplicated cases of osteitis deformans have not been reported. Even with an incidence of 2 per cent, Speiser⁶ expressed the belief that sarcoma

* Submitted for publication, Feb. 1, 1931.

* From the Henry Baird Favill Laboratory and Surgical Service "A" of St. Luke's Hospital.

1. Paget, James: On a Form of Chronic Inflammation of Bones, *Tr. Med.-Chir.*, London **60**:37, 1877.

2. Bird, C. E.: Sarcoma Complicating Paget's Disease of the Bone, *Arch. Surg.* **14**:1187 (June) 1927.

3. Da Costa, J. C.; Funk, E. H.; Bergeim, O., and Hawk, P. B.: Osteitis Deformans, *Pub. Jefferson M. Coll. & Hosp.* **6**:1, 1915.

4. Packard, F. A.; Steele, J. D., and Kirkbride, T. S.: Osteitis Deformans, *Am. J. M. Sc.* **122**:552, 1901.

5. Higbee, W. S., and Ellis, A. G.: A Case of Osteitis Deformans, *J. M. Research* **24**:43, 1911.

6. Speiser, F.: Sarkomatöse Entartung bei der Ostitis deformans, *Arch. f. klin. Chir.* **149**:274, 1928.

occurs about thirty times more frequently in combination with Paget's disease than statistics dealing with the occurrence of sarcoma of the bone in general would lead him to expect.

REPORT OF A CASE

J. C. D., a white man, aged 66, when first admitted to St. Luke's Hospital on Dec. 7, 1928, complained of dull, aching pains of several years' duration between the scapulae, along the spine, in both hips and in the left leg. For ten years he had



Fig. 1.—The medial side of the left leg.

noticed that his legs were slowly bowing outward, and about fifteen months before entering the hospital he had bruised the left shin. Pain and tenderness persisted and gradually became severe. The roentgenograms demonstrated a cystlike region in the left tibia at the junction of the middle and lower third of the bone, which otherwise showed the changes usually found in osteitis deformans. Seven years previously the right femoral vein was thrombosed, and because of blood-stained sputum a diagnosis of infarct of the lungs had been made. Since then there had been progressive muscular weakness and dyspnea on physical exertion. No other instances of Paget's disease had occurred in the family. The cyst of the bone was curetted and drained; it contained only a small amount of changed blood. As the pain in the left leg did not subside, the patient returned to the hospital, and on

Oct. 7, 1929, Dr. L. L. McArthur reopened the tissues and curetted out several pieces of opaque white tissue of the consistency of a hyperplastic lymph node which were diagnosed as osteogenic sarcoma. The examinations of the blood made at this time disclosed: 4,530,000 erythrocytes, 91 per cent hemoglobin and 13,900 leukocytes per cubic millimeter. The calcium of the blood varied from 11.09 to 12.2 mg. per hundred cubic centimeters of serum and the phosphorus from 3.83 to 3.9 mg. per hundred cubic centimeters. The excretion of calcium in the urine varied from 0.142 to 0.217 Gm. per twenty-four hours, while the inorganic phosphorus excreted was about 0.6 Gm. No changes were observed in the urine. The patient was discharged four days after admission and returned on December 2, the tumor having increased in size. On the following day, Dr. L. L. McArthur amputated the left leg near the middle of the thigh. Except for a slight post-operative fever, the patient recovered rapidly from the operation and was discharged on December 24. He died outside of the hospital on Aug. 10, 1930, and although a postmortem examination was not made, clinically there were no metastases and no recurrence of the sarcoma.

The following descriptions are taken from laboratory records of the hospital as reported by Dr. Edwin F. Hirsch. The material removed from the growth in the left tibia by Dr. L. L. McArthur on Oct. 7, 1929, was embedded and cut by the paraffin method, and sections were stained with hematoxylin and eosin and phosphotungstic acid-hematoxylin. Histologically, the growth consisted of mesoblastic tissue, the cells of which were closely laid together in a mosaic. They had an abundant granular cytoplasm and large oval vesicular nuclei with large granules of chromatin. In the interstices between the cells there was a variable amount of hyaline substance. In edematous regions where the cells were more widely separated, the matrix was laid down in coarse fibrils and showed marked affinity for the purple of the hematoxylin and eosin stain. Small masses of necrotic bone were irregularly distributed. Many cells were in active mitosis. In sections stained with phosphotungstic acid-hematoxylin the hyaline matrix had an orange-red color like that of bone.

The left leg was amputated above the knee. There were two defects of the skin above the knee where flaps had been cut away, and the tissues included the distal 8 cm. of the femur. The cortex of the femur at the level of amputation was 1.5 cm. in thickness, and the medullary canal was 1.4 cm. in diameter. The medullary tissues were soft red marrow supported in a meshwork of narrow bone trabeculae. There was an ovoid swelling in the tissues of the lower part of the leg, the center of which was 9 cm. above the internal malleolus. The skin over this swelling was ulcerated in a region 4 by 3 cm., and the margins of the ulcer were raised about 1.5 cm. above the surrounding tissues of the skin. Beneath the ulcer was a hard mass firmly attached to the bone, and when the soft parts were stripped away there was an anterior bowing of the tibia equal to about 3 cm. On the surfaces made by bisecting the tibia sagittally the new growth involved the shaft of the bone in its entire thickness and circumference; it was about 8 cm. in diameter. The white granular tumor tissue was mottled with a few small hemorrhages. The thickness of the cortex of the tibia immediately above and below the tumor was 1.2 cm., and the bone was coarsely porous and soft. The cortex gradually thinned out proximally so that just below the knee the thickness was about 0.5 cm. The marrow canal was 1 cm. in diameter near the tumor and it widened proximally as the cortex decreased in thickness. The periosteum over the thickened cortex was as thick as 3 mm. The articular cartilages of the tibia were unchanged, and the lymph nodes in the popliteal space were not enlarged.



Fig. 2.—The inner half of the left tibia after it has been divided longitudinally in the sagittal plane. The cortex of the shaft is coarsely porous and increased in thickness.

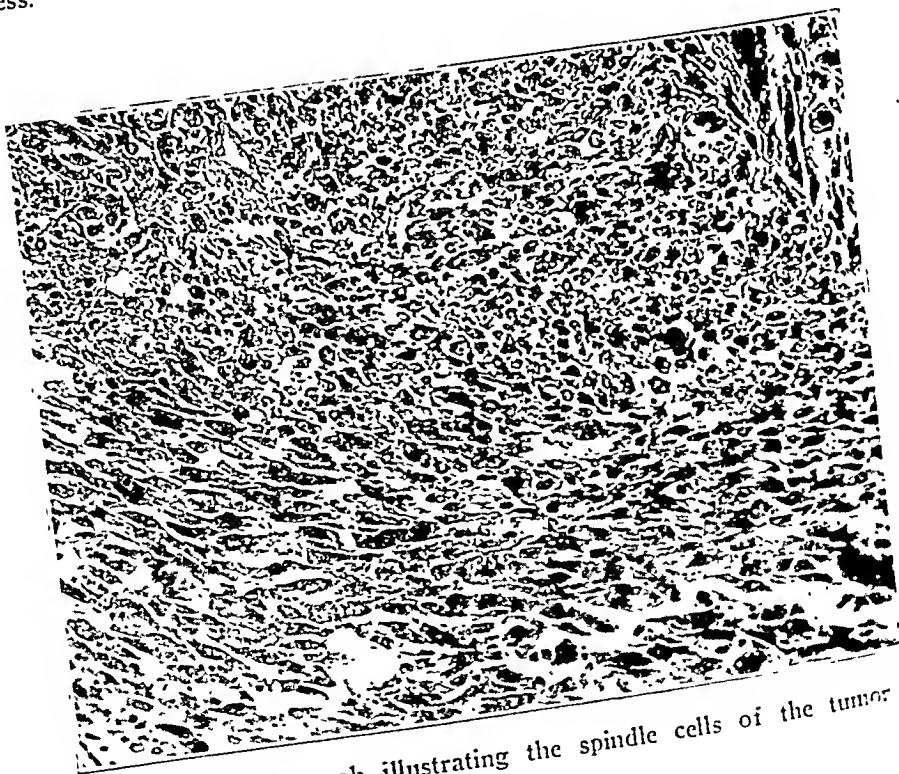


Fig. 3.—Photomicrograph illustrating the spindle cells of the tumor tissue beneath the skin.

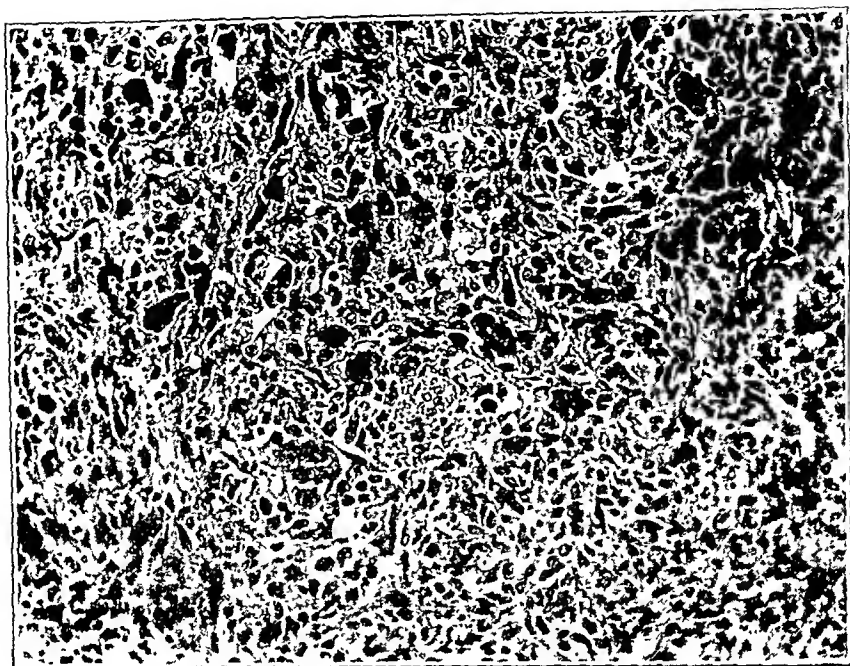


Fig. 4.—Photomicrograph illustrating myeloid giant cells in certain portions of the tumor.

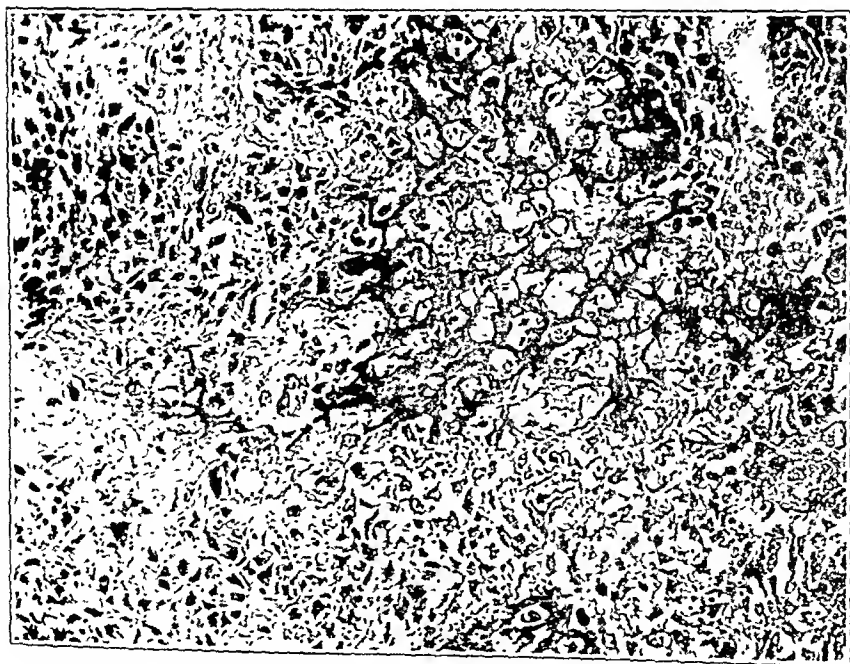


Fig. 5.—Photomicrograph of osteoid tissue in the tumor.

Histologically, the tissues from the tumor under the skin were compact masses of spindle and oval cells with a scant fibrous stroma. The cytoplasm of the cells was light pink, finely granular and abundant; the nuclei varied considerably in size, shape and chromatin content, and many cells were in mitosis. Giant cells were scattered singly or in groups in the tissues; most of them had four or five nuclei, but some had twenty. The tumor was moderately vascular, and the capillaries were surrounded by masses of tumor cells. Portions of the tumor were necrotic and infiltrated with polymorphonuclear leukocytes. Tissues taken from the marrow canal closely resembled those from the mass under the skin, except that they contained regions of osteoid tissue. In sections of the cortex taken from the tibia just above the tumor, the spongy bone consisted of narrow irregular trabeculae and spicules. The edges of the trabeculae of the bone were extensively eroded, and in many of the crypts there were myeloid giant cells. The trabeculae were covered by a narrow layer of osteoblasts. A loose, irregularly arranged fibrous tissue containing a few scattered fat cells were supported by this bony framework. There were also many dilated, thin-walled capillaries, and in some places, masses of plasma cells and lymphocytes as in chronic inflammation.

All of the writers who have reported cases of sarcoma in bones with osteitis deformans agree that the relation between the two diseases is more than a mere coincidence. Gruner, Scrimger and Foster⁷ stated that the chief difference histologically between the tumor tissue and the fibrous tissue between the trabeculae of the diseased bone is the apparent unrestrained growth of the former and that the tumor growth seems to be added to an already altered osseous tissue. Von Albertini,⁸ in a report on the pathologic process in Speiser's case stated that the marrow in the bones affected by Paget's disease was in many places converted into a cellular sarcomalike tissue composed of large spindle cells. This tissue did not invade or destroy the surrounding structures, and von Albertini¹ considered it an intermediate stage between the chronically inflamed fibrous marrow and the associated polymorphocellular sarcoma. He concluded that while osteitis deformans may not necessarily be a presarcomatous disease, in some instances it may give rise to pre-sarcomatous tissue. In the case reported by Fedder⁹ there were multiple tumors in the diseased bones. As the normal bones were not involved, Fedder⁹ suggested that the affected bones had undergone malignant degeneration in many places. Speiser's patient attributed the onset of the tumor to a trauma, but von Albertini⁸ believed that the chronic inflammatory changes in the bone marrow were of far greater etiologic importance. On the basis of roentgen and histologic examinations.

7. Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: A Clinical and Histological Study of a Case of Paget's Disease of the Bones with Multiple Sarcoma Formation, *Arch. Int. Med.* 9:641 (June) 1912.

8. von Albertini, A.: Ueber Sarkombildung auf dem Boden der Ostitis deformans Paget, *Virchows Arch. f. path. Anat.* 268:259, 1928.

9. Fedder, L.: Ostitis deformans mit sekundären Rundzellensarcomatose, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 31:391, 1924.

Stöhr¹⁰ concluded in his report that a pathologic fracture of the bone was the stimulus that gave rise to a polymorphocellular sarcoma.

About 22 instances of sarcoma involving bones affected by Paget's disease have been reported; 19 of these cases occurred in men and 3 in women. The ages of the patients ranged from 36 to 72 years; the average age was about 55. The time elapsing between the onset of Paget's disease and the appearance of the sarcoma was frequently unknown, but in 7 of 12 patients, osteitis deformans was known to have existed for ten or more years. In several instances, Paget's disease of the bone was not suspected until it was demonstrated by roentgenograms of the tumor. In 6 cases there was a definite history of trauma.

All of the tumors described by Bird² were fibrosarcomas with more or less production of bone and giant cells. He considered the giant cell tumors reported by Packard, Steele and Kirkbridge⁴ and by Heazlitt¹¹ as new growths of this nature. The tumor reported by Gruner, Scrimger and Foster⁷ was an osteogenic sarcoma and that reported by Fedder,⁹ a round cell sarcoma, while the bone described by Ransohoff¹² was diagnosed as a mixed cell sarcoma. Most of the tumors grew rapidly and metastasized widely.

It is interesting to note in the case herein reported that the concentration of phosphorus in the blood was within normal limits, and the amount of calcium in the blood was only slightly elevated.

SUMMARY

A review of the literature discloses that sarcoma is a relatively frequent complication of osteitis deformans (Paget's disease), although only about twenty-two reports concerning this condition include a complete pathologic description.

Sarcoma of the left tibia, developing in a patient who had had Paget's disease for ten years preceding the appearance of the tumor, is described.

10. Stöhr, F.: Ueber Sarkombildung bei Ostitis deformans Paget, Wien. med. Wehnschr. **79**:1231, 1929.

11. Heazlitt, L.: Sarcoma Complicating Primary Paget's Disease of the Bone, New York State J. Med. **17**:330, 1917.

12. Ransohoff, J.: Osteitis Deformans, Central Sarcoma, Streptococcus Infection, Lancet-Clinic **110**:672, 1913.

CONGENITAL MALFORMATIONS OF THE INTESTINAL TRACT AND BILE DUCTS IN INFANCY AND IN CHILDHOOD*

WARREN H. COLE, M.D.

ST. LOUIS

In a series of 45,000 admissions to the St. Louis Children's Hospital during the past fifteen years there have been 81 instances (see table) of congenital malformation of the intestine and bile ducts. Obviously, most of the lesions herein described occurred in new-born infants, many of whom were admitted from the maternity wards of Barnes Hospital.

Although hypertrophic pyloric stenosis, as seen in infants, is dependent on a congenital cause, it will not be discussed in detail since a review of the cases occurring in this clinic was recently made by Clopton and Hartmann.¹ They reported a total of 81 cases in which an operation was performed. The history in these cases is usually typical. The first two or three weeks of life may be uneventful or broken by an occasional attack of vomiting. During the third or fourth week the obstruction becomes most marked and the vomiting is practically always projectile. A tumor may or may not be felt. Peristalsis can usually be demonstrated, especially after feeding. The occurrence of dehydration and alkalosis may be rapid. Clopton and Hartmann strongly emphasized the fact that an operation should never be considered until these two factors are controlled by "combined" solution, dextrose, transfusions, etc. The method of administration of Hartmann's combined solution is given elsewhere. The most remarkable feature of their report is the reduction of the mortality to 4 per cent in the last 50 cases. The correction of dehydration and alkalosis along with the careful specific operative technic advocated by Clopton probably accounts for this sharp reduction in mortality. The operation is performed on an improvised hot water table after the extremities have been wrapped with roll cotton. Rarely does the local anesthetic (025

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* From the Department of Surgery, Washington University School of Medicine, and St. Louis Children's Hospital.

* The cases reported are from the service of Dr. M. B. Clopton, at whose suggestion the work was undertaken. Dr. W. McKim Marriott allowed the inclusion of many cases from the medical service of the St. Louis Children's Hospital.

1. Clopton, M. B., and Hartmann, A. F.: The Fredet-Rammstedt Operation for Congenital Pyloric Stenosis, *Surg., Gynec. & Obst.* **47**:527, 1928.

per cent procaine hydrochloride) have to be supplemented by a general anesthetic, especially if the incision is made high on the right side so that the liver aids in preventing evisceration. The tumor is split by a blunt dissector longitudinally over an avascular area down to the submucosa, until the normal tough intestinal or gastric wall is encountered on each end. Just before one ties the last suture in the peritoneum, from 100 to 150 cc. of physiologic solution of sodium chloride, Ringer's solution or combined solution should be introduced into the peritoneal cavity. About four hours after operation, water and feedings are allowed, from $\frac{1}{2}$ to 1 ounce, and gradually increased to normal by the third or fourth day. The details of the care of the infants and technic of operation are given by Clopton and Hartmann.

Since intussusception is not dependent on an obvious congenital deformity that can be visualized, this subject will also be omitted in the present survey. In a recent publication, Clopton² emphasized the importance of making an early diagnosis in these cases, since the mortality figures increase rapidly with the duration of symptoms. In a review of the literature on intussusception he was able to find only a few cases in which the patient survived operation when a resection was necessary. On the other hand, when the intussusception had been present only a few hours and there was no gangrene, few deaths occurred.

MALFORMATION OF THE INTESTINE

Incidence.—Perhaps the first instance of malformation of the intestine is that reported by Calder³ in an infant with atresia of the duodenum. In 1912, Spriggs⁴ made an exhaustive study of the subject, assembling the reports of 328 cases from the literature (excluding occlusions of the pylorus and anus). He made a thorough study of the possible etiologic factors. In 1922, Davis and Poynter⁵ collected the cases of intestinal atresia reported in the literature, recording a total of 401, and classified them as follows, according to the area involved: duodenum, above the papilla, 59 cases; duodenum, below the papilla, 75; jejunum, 60; ileum and cecum, 101; colon, 39, and multiple atresia, 67. From their classification it can be seen that in almost exactly 33 per cent of cases the atresia occurred in the duodenum.

2. Clopton, M. B.: Intestinal Obstruction in Infants, *J. Missouri M. A.* **25**: 137, 1928.

3. Calder, J.: Medical Essays and Observations, Edinburgh, Philosophical Society **1**:203, 1733; quoted by Davis and Poynter (footnote 5).

4. Spriggs, N. I.: Congenital Intestinal Occlusion, *Guy's Hosp. Rep.* **66**:143, 1912.

5. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestines, *Surg., Gynec. & Obst.* **34**:35, 1922.

By combining the reports of Quinland⁶ and von Koos,⁷ Thorndyke⁸ found an incidence of 1 case of atresia of the intestinal tract to 9,288 births in a series of 371,541 births. Two instances of complete atresia of the intestine (duodenum and terminal ileum) were encountered in 6,300 births occurring in the maternity wards of Barnes Hospital. It must be remembered, however, that the foregoing figures deal only with atresia and that the occurrence of stenosis or partial occlusion by bands, etc., is far more frequent than that of atresia. Atresia at the pylorus apparently is rare. I was able to find reports of only four cases in the literature.

Morbid Anatomy.—Four different types of obstruction due to congenital malformation are recognized: (1) Peritoneal Bands: This is perhaps the one most frequently encountered. In many instances the obstruction is only partial, and occasionally the patient may grow to maturity before the condition requires operative intervention. These bands are perhaps more frequently encountered in the ileocecal region and about the duodenum than anywhere else. Although the impression might be gained that the bands are secondary to inflammatory processes, I am inclined to believe that they are dependent on embryonic defects, such as an excessive deposit of tissue at points of fixation (e. g., the duodenum) or abnormal fixation of embryonic structures which normally are obliterated before birth. (2) Stenosis: This type is frequently encountered, usually revealing a narrowing of the bowel over a variable distance with constriction of the lumen to a size barely admitting a probe. Occasionally the stenosis is so marked that nothing more than a fibrous cord intervenes between the segments of normal bowel. Usually the stenosis extends over a distance so great that an anastomosis is necessary to correct the defect, but in two of the present cases the stenosed portion (pylorus and terminal ileum) was so short that a Mikulicz operative procedure was sufficient to relieve the obstruction. (3) Atresia: Occasionally the termination of normal bowel is so abrupt that a blind loop is formed, usually without tissue (such as a fibrous cord) intervening between the segments of normal bowel. About 15 per cent of atresias of this nature are multiple. (4) Diaphragm: In the duodenum and ileocecal region, rarely elsewhere, a diaphragm of tissue is occasionally found which abruptly breaks the continuity of the lumen. The patency of the lumen is regained immediately distal to the diaphragm. In some instances this diaphragm has

6. Quinland, W. S.: Congenital Malformation of Intestine: Atresia and Imperforate Anus, Boston M. & S. J. **187**:870, 1922.

7. von Koos, A.: Congenital Atresia of the Duodenum, *Jahrb. f. Kinderh.* **93**:240, 1920.

8. Thorndyke, A.: Duodenal Atresia and Stenosis in Infancy, Boston M. & S. J. **196**:763, 1927.

no opening to allow passage of the intestinal contents; usually, however, an opening is present. Cannon and Halpert⁹ recently reported a case of perforated diaphragm of the duodenum in a girl, 8 years of age, whose death presumably was caused by a rupture of the stomach which, in turn, was probably produced by the administration of enemas containing excessive amounts of fluid. They were able to find the records of five cases in which there was complete obstruction produced by an imperforate diaphragm interrupting the lumen of the duodenum at about the level of the papilla of Vater. As far as Cannon and Halpert could determine, only two cases besides their own had been reported in

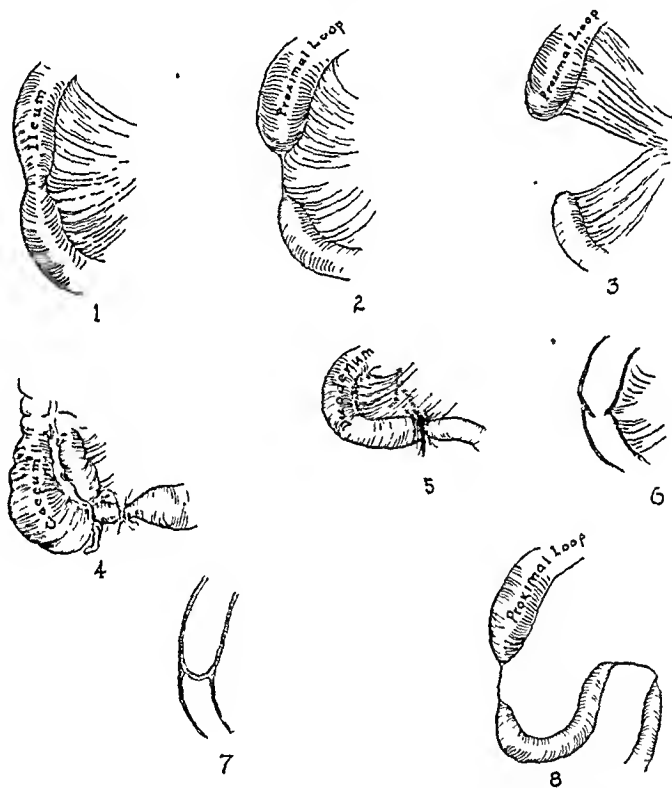


Fig. 1.—Congenital malformations occurring in the intestine: (1) stenosis with partial obstruction; (2) occlusion with a blind loop; (3) blind loop with a gap in the mesentery; (4) obstruction by a fibrous band (found usually in the third part of the duodenum or the terminal ileum); (5) obstruction at the ligament of Treitz; occasionally an anomalous superior mesenteric artery is the chief factor in producing the destruction (see report of cases); (6) cross-section of intestine showing perforated diaphragm; this occurs usually in the duodenum or the terminal ileum; (7) cross-section of imperforate diaphragm, and (8) multiple occlusion of the ileum or jejunum; this constitutes about 15 per cent of the atresias of the intestine. Clinically, the dilatation of the proximal loop with collapse of the distal loop, is usually even more pronounced than shown in the illustration.

9. Cannon, P. R., and Halpert, Béla: Congenital Stenosis of the Third Portion of the Duodenum with Acute Occlusion and Rupture of Stomach, *Arch. Path.* 8:611 (Oct.) 1929.

which the opening in the congenital diaphragm was so small that obstruction was produced when the child's diet was changed from liquid to solid food. (5) Defective Rotation: Innumerable possibilities exist for the production of obstruction because of incomplete or defective rotation. Anomalies of this kind were thoroughly discussed by Dott.¹⁰

Etiology.—Numerous theories have been expressed in an attempt to explain the production of the various occlusions found. To understand them fully and to attach proper importance to the respective theories, a brief discussion regarding the embryology of the intestine should be included here. Until the fifth week of fetal life the alimentary tract in the human embryo is a straight tube. Shortly afterward the tube becomes curved. From the upper loop (duodenal) two outgrowths appear: an anterior one, which forms the liver, and a posterior one, which gives rise to the pancreas. The omphalomesenteric (vitelline) duct serves as an avenue of communication between the alimentary tract and the yolk sac early in embryonic life, but becomes obliterated some time during the third or fourth month. Persistence of the intra-abdominal portion of the vitelline duct gives rise to a Meckel's diverticulum.

1. Bland-Sutton's Theory: Perhaps the most acceptable theory of the formation of intestinal occlusions is that offered by Bland-Sutton,¹¹ who claimed that they occur at the site of embryologic events. Accordingly, one can readily understand that if the anal pit (proctodeum) fails to unite with the hindgut, an imperforate anus results. Likewise, if the stomodeal invagination that forms the mouth does not unite with the foregut an imperforate pharynx results. Should the process of closure of the base of the vitelline duct proceed too far in the ileum during fetal life, an occlusion in the terminal ileum would be found after birth. Obviously, the location of Meckel's diverticula must be clearly established before one can offer that condition as a factor in the production of lesions in the ileocecal region of the distal portion of the ileum. In an anatomic study Lamb,¹² discovered that only two fifths of the cases of Meckel's diverticula occurred in that portion of ileum within 1 foot of the ileocecal valve. Bland-Sutton also remarked that duodenal diaphragms occur at the point where the diverticulum issues to form the liver and the pancreas. It seems possible that many of the duodenal bands and occlusions caused by excessive fixation might be due to incomplete absorption of the stem processes that support the liver and the pancreas as they bud forth from the duodenum early in fetal life. Snaring of loops of bowel at the umbilicus during fetal life

10. Dott, N. M.: Anomalies of Intestinal Rotation, *Brit. J. Surg.* **11**:251, 1923-1924.

11. Bland-Sutton, J.: Imperforate Ileum, *Am. J. M. Sc.* **98**:457, 1889.

12. Lamb, D. S.: The Meckel Diverticulum, *Am. J. M. Sc.* **105**:633, 1893.

should probably be included under the same heading. Obviously, if the umbilical ring should close too rapidly, the circulation of part or all of the loop outside the peritoneal cavity would be cut off. In this event, it seems plausible that there would be an atrophy of that part, resulting in an atresia or stenosis.

2. Vascular Defects: It was suggested by Jaboulay¹³ and Wyss¹⁴ that in many instances intestinal atresia or stenosis is due to defects in the vascular supply of the intestine. Little and Helmholz¹⁵ encountered a case of atresia of the pylorus that, in their opinion, was produced by a defective arterial supply, including absence of the following arteries: pancreaticoduodenalis superior, gastro-epiploica and the pyloric branch of the hepatic artery. In my estimation vascular anomalies serve as the chief mechanism in the production of atresia and stenosis in more cases than is ordinarily considered.

3. Defective Intestinal Rotation: Dott presented a thorough description of the mechanism of rotation and the types of obstruction produced. Many instances of volvulus occurring at the time of birth are caused by lack of fixation of parts (e. g., the ileocecal region) or excessive length of the mesentery in certain areas. It seems possible that obstruction by peritoneal bands might be part of an excessive fixation occurring during the process of rotation. In rare instances reversed rotation takes place (in a clockwise direction), placing the transverse colon posterior to the duodenum and constricting the colon by mesentery. If excessive rotation takes place, the loop of bowel at the stem of the involved loops will be obstructed and perhaps injured by a defective blood supply. However, most cases of defective rotation produce no obstruction.

4. Miscellaneous Causes: Numerous theories have been mentioned, which individually do not seem as important as the ones mentioned when considered as causes of obstruction. Tandler¹⁶ described an excessive amount of epithelial cells occurring in the duodenum of 30 to 60 day embryos. Under such circumstances it seems possible that the diaphragm found within the lumen at this site might be produced by failure of these areas of epithelial proliferation to disappear completely. Another factor that has been mentioned as a possible cause of intestinal atresia and stenosis is fetal peritonitis. Although it is known to occur, I feel that its importance in the production of atresia has been exag-

13. Jaboulay: *Chirurgie des centres nerveus*, Paris, O. Doin, 1902, vol. 2, p. 43; quoted by Spriggs (footnote 4).

14. Wyss: *Beitr. z. klin. Chir.* **26**:631, 1900; quoted by Spriggs (footnote 4).

15. Little, H. M., and Helmholz, H. F.: *Situs Transversus and Atresia of the Pylorus*, *Bull. Johns Hopkins Hosp.* **16**:249, 1905.

16. Tandler: *Morphol. Jahrb.* **29**:187, 1902; quoted by Spriggs (footnote 4).

gerated, since it seems unlikely that a stricture would be found in the absence of other signs of peritonitis. Moreover, except in syphilitic persons, the occurrence of peritonitis or intestinal ulceration in fetal life must be extremely rare. Intussusception and volvulus, with subsequent atrophy of the loop of bowel involved, have been mentioned as possible causes of atresia or stenosis.

Diagnosis.—Perhaps the most constant symptom of intestinal obstruction of congenital origin is vomiting. It usually begins within twenty-four hours, but occasionally may be delayed two or three days, especially if the obstruction is not complete. As Cameron¹⁷ emphasized, persistent vomiting of bile-stained material in a newly born child should always arouse the suspicion of duodenal obstruction. Occasionally the first vomiting will be profuse and consist of amniotic fluid. This is pathognomonic of obstruction if present, but the absence of vomitus consisting of amniotic fluid cannot be used as an argument against obstruction. Usually the vomiting is forceful, especially in the later periods of obstruction. When the obstruction is high, food is usually vomited immediately after the feedings in contrast to the occurrence of delayed vomiting in obstruction at low levels. The vomitus may or may not contain bile, depending on the location of the obstruction. Unless accessory bile ducts are present, there can be no bile in the vomitus if the obstruction is proximal to the ampulla of Vater. When the obstruction is distal to the ampulla, the vomitus usually is bile-stained and contains a moderate amount of mucus. Blood is rarely present in either instance.

Examination of the stools also offers a source of information in regard to diagnosis. An absence of bile in the meconium is pathognomonic of complete obstruction of the bowel distal to the ampulla. Many cases have been reported, however, in which the stools contained bile in spite of the fact that operation revealed a complete obstruction distal to the ampulla of Vater. Since the liver begins excreting bile at about the fourth month, it can readily be understood that the meconium could be bile-stained for at least a day or two, provided the obstruction occurred later in fetal life than the onset of biliary secretion. If the obstruction is complete, the normal change from greenish meconium to stools containing digested milk will not occur. Constipation is usually present and at times is practically absolute. Frequently, it will be of value to examine the meconium for the presence of bacteria. If complete obstruction is present, there will be no bacteria in the meconium. Auscultation over the abdomen may occasionally be of aid in determining the site of obstruction. If the obstruction is low, gurgling

17. Cameron, H. C.: Some Forms of Vomiting in Infancy, *Brit. M. J.* 1:765. 1925.

sounds and borborygmus are usually heard, whereas if the obstruction is in the duodenum no normal sounds are apt to be encountered.

Roentgenography is a valuable aid in diagnosis, and should be resorted to immediately if the diagnosis of obstruction is not certain. Fluoroscopic examination after the oral administration of barium sulphate is probably of more aid than roentgenograms when the obstruction is only partial. The determination of gastric retention by roentgenography is a simple procedure and in cases of duodenal obstruction is pathognomonic. However, an "open plate" of the abdomen without an opaque meal should be taken first. If the obstruction is at least a few feet beyond the duodenum, the pattern of gas outlining the enormously distended intestines will be seen plainly. This intestinal pattern of gas is constantly seen in cases of complete obstruction.

Examination of the abdomen usually reveals peristaltic waves. If the diagnosis is doubtful, observations for waves should be made on numerous occasions, especially at short intervals after feeding. Distention is present in those instances in which the obstruction is low, but in cases of duodenal obstruction it may be absent. Masses are rarely felt unless congenital cystic tumors are present. Palpation usually reveals little tenderness or muscle spasm. After the first day or two emaciation, dehydration and loss of weight proceed rapidly. Tachycardia and cyanosis soon manifest themselves as evidence of the infant's critical condition.

Neff and Haden¹⁸ reviewed the chemical indications in the blood in cases of obstruction in the new-born infant. They stated that a lowering of the chloride content of the blood and an increase in the carbon dioxide-combining power occur early, even before the rise in nonprotein nitrogen of the blood that is diagnostic of obstruction. Alkalosis is the usual indication, although acetone bodies are sometimes found in the blood.

The length of life and severity of symptoms depend on various factors. In my experience, however, the location of the obstruction does not exert the influence on severity of symptoms that it does in adults. Obviously, if the obstruction is incomplete, the diagnosis may be difficult. Frequently, symptoms do not manifest themselves for weeks, months or even years. For this reason it may be difficult, on certain occasions, to differentiate obstruction caused by congenital malformation from that produced by hypertrophic pyloric stenosis if the symptoms appear during the fourth or fifth week of life. Since the onset of symptoms of hypertrophic pyloric stenosis occurs so regularly between the third and sixth week of life, it can usually be excluded

18. Neff, F. C., and Haden, R. L.: Congenital Transduodenal Bands, *Am. J. Dis. Child.* 30:82 (July) 1925.

and a diagnosis of obstruction of congenital origin be made when the onset occurs before the third week of life.

Treatment.—Before operative intervention is resorted to, the dehydration and chemical changes in the blood must be corrected as far as possible. Administration of physiologic solution of sodium chloride or Ringer's solution subcutaneously will serve adequately to restore the water deficiency, but is not entirely efficacious in correcting the changes in the blood that may be present. As a means of combating these changes, Hartmann¹⁹ has probably offered the best contribution in the form of a "combined solution" which he uses in alkalosis as well as acidosis because of its buffer action. The solution consists of sodium chloride, potassium chloride, calcium chloride and sodium lactate and may be administered subcutaneously, intravenously or intraperitoneally. Conversion of the lactate into bicarbonate takes place so slowly that a favorable buffer action is obtained (unless severe renal damage is present) even in alkalosis, which is the change most frequently encountered in intestinal atresia.

I operate on all infants on an improvised hot water table; as an additional measure to prevent chilling and shock, I wrap the extremities with cotton. The operation should be started under local anesthesia (0.25 per cent procaine hydrochloride) and ether administered only when absolutely necessary to obtain relaxation or prevent shock from pain. Allowing the baby to suck on a holeless nipple will at times eliminate restlessness during the entire operation. Before the abdomen is closed, it is a good practice to introduce from 150 to 200 cc. of Ringer's solution, physiologic solution of sodium chloride or "combined solution" through a catheter as the last stitch is being placed in the peritoneum.

In spite of the fact that the mortality is extremely high in cases of atresia of the intestine, operation should be resorted to as soon as the diagnosis is made and dehydration is corrected, since there can be no hope of recovery without operation. Obviously, it is extremely important that the diagnosis be made as early as possible whether the obstruction is complete or not. Opinions vary as to the type of operation to be resorted to in atresia of the intestine. As long ago as 1904, before any operative cures had been reported, Clogg²⁰ suggested that intestinal anastomosis was to be preferred to simple enterostomy as an initial procedure. His assumption was that the infant does not tolerate the exclusion of the distal intestinal segment because of the short length of the intestine left for absorption. Along with Clogg, Davis and

19. Hartmann, A. F.: Acidosis, Alkalosis and Dehydration, *Colorado Med.* 26:373 (Nov.) 1929.

20. Clogg, H. S.: Intestinal Atresia, *Lancet* 2:1770, 1904.

Poynter, Richter²¹ and others, I am inclined to believe intestinal anastomosis is the procedure of choice in atresia of the small intestine unless the infant is too ill to endure the operation. If the infant is extremely ill it is probably justifiable merely to drain the bowel, but plans should be made to perform an anastomosis within two or three days. If the child dies before this time has elapsed or does not rally, he probably would not have tolerated a primary entero-anastomosis. However, when the atresia is located in the colon, a colostomy may become the procedure of choice, followed later by anastomosis. Further support to the advocacy of anastomosis is lent by clinical results. As far as I am able to determine, only three patients with atresia of the intestine have survived. Fockens,²² Ernst²³ and Richter each reported successful results in a case. Each of these surgeons had performed a primary intestinal anastomosis of some sort. Apparently, there have been no cures following a primary enterostomy done with the intention of performing anastomosis later, except in cases of imperforate anus. It is somewhat difficult to explain this extremely high mortality. Clogg quoted several cases in which the patients had undergone intestinal anastomosis of a satisfactory nature, but all of them had died. Autopsy revealed that the constricted lumen of the distal portion of intestine had refused to allow the passage of any intestinal content. Whether this was due to the inadequate size of the lumen of the intestine or to the fact that peristalsis was abnormal or absent could not be determined. To obviate this complication some operators have recommended that the distal portion of intestine should be dilated with fluid at the time of operation. I am not convinced of the efficacy of this procedure because the dilation produced in this manner should not have any material influence on the restoration of peristalsis, nor should it be permanent, so far as I can determine. It must be remembered that the remarks regarding the appalling mortality apply only to atresia and not to partial occlusions.

In complete obstruction, the type of anastomosis is determined by the type of defect found. I believe that when the atresia is found in the duodenum, an ordinary gastro-enterostomy is the operation of choice. Should the atresia be lower down in the small intestine or in the colon, a lateral anastomosis probably represents a much easier and safer procedure than any other. When the obstruction is produced by peritoneal

21. Richter, H. M.: *Surgery of the Gastro-Intestinal Tract in Children*, in Abt: *Pediatrics*, Philadelphia, W.B. Saunders Company, 1924, vol. 3, p. 513.

22. Fockens, T.: Over aangenore atresia van den darm met een door operatie genogen gevol, *Nederl. tijdschr. v. geneesk.* 1:1658 (Aug.) 1911; quoted by Richter (footnote 21).

23. Ernst, N. P.: A Case of Congenital Atresia of Duodenum Treated Successfully by Operation, *Brit. M. J.* 1:644, 1916.

bands, cutting the band usually suffices. The intestine beneath the band should be inspected closely, however, since a stenosis is commonly found associated with adhesive bands. Occasionally the area of stenosis is so short that a plastic operation of the Mikulicz type will be all that is necessary. This type of repair was found to be the procedure of choice in a case in the present series in which Dr. M. B. Clopton operated. The stenotic area was only 1 or 2 cm. long and was situated in the terminal ileum near the ileocecal valve. If the stenosis involves more than 2 or 3 cm. of the intestines, an entero-enterostomy must be performed, but resection of the stenosed area is not necessary. If multiple points of atresia are found, the condition become practically hopeless, but if the infant's condition permits, anastomosis should be performed at the various sites of atresia.

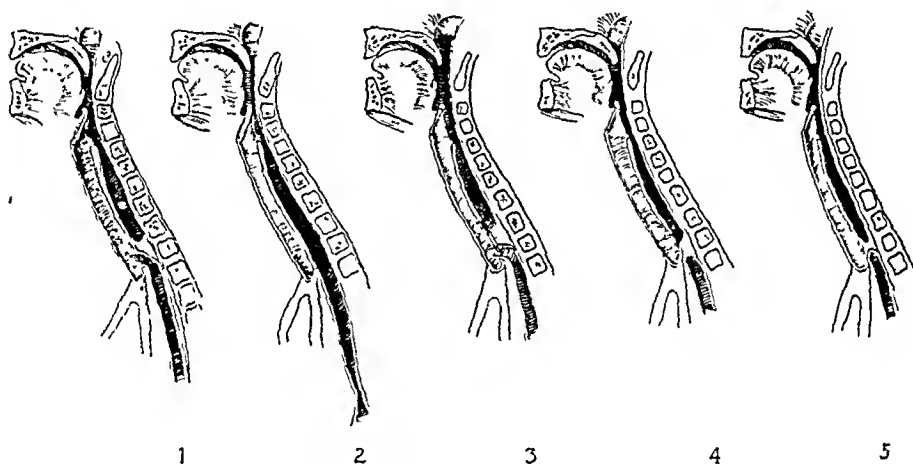


Fig. 2.—Types of congenital malformation of the esophagus: (1) the type in which the proximal portion ends blindly, the distal portion communicating with the trachea; this type is found in from 80 to 90 per cent of the anomalies; (2) constriction without atresia, usually occurring at the distal end of the esophagus; (3) communication between the trachea and each segment of the esophagus; (4) communication between the trachea and the proximal segment (rare), and (5) atresia of the esophagus without a tracheal fistula.

ANOMALIES OF THE ESOPHAGUS

Defects of the esophagus may be classified into five groups. A better understanding of the various defects can be obtained from figure 2 than from a description. Atresia is encountered more often than stenosis. By far the most common anomaly is atresia with dilatation of the proximal end of the esophagus (90 per cent of all atresias of the esophagus belong in this class). Probably the next in frequency is the type having tracheal communication with both ends of the esophagus.

The remaining three types are relatively rare. Plass,²⁴ who conducted a thorough anatomic study of esophageal defects, noted that the tracheal fistulas usually occurred only 1 or 2 cm. above the bifurcation of the trachea.

The diagnosis of anomalies of the esophagus is usually not difficult. When atresia exists, the child is able to swallow only a few mouthfuls. As more is taken the food is regurgitated through the mouth and nose. Usually attacks of coughing, asphyxia and cyanosis accompany this regurgitation. A nasal catheter is arrested from 3 to 10 cm. beyond the pharynx. When a tracheo-esophageal fistula exists, as is usually the case, an aspiration pneumonia is practically inevitable and the child dies a few days after birth. I was unable to find a record of the survival of a single patient with atresia of the esophagus when a tracheo-esophageal fistula accompanied the condition.

From the standpoint of treatment, few suggestions can be offered. Obviously an enterostomy of some type is a necessary procedure to supply the infant with food. Theoretically, a jejunostomy would be more advisable than a gastrostomy because food fed through a tube in the jejunum would be less likely to regurgitate into the tracheo-esophageal fistula that is present in a great percentage of cases. In the cases that Plass reviewed, he encountered an instance in which jejunostomy had been done, but the infant died. In view of the fact that gastrostomies have been universally fatal, I feel justified in advising jejunostomy instead of gastrostomy in these cases. Obviously subcutaneous or intraperitoneal administration of fluid, as previously described, must be resorted to as soon as the diagnosis is made. Attempts have been made to ligate the fistulous connection, but no successful cases have been reported. Death usually intervenes in from four to eight days after birth. Pneumonia is practically always encountered at autopsy.

I have an additional suggestion to offer. As far as I have been able to determine, every fatality in esophageal atresia has been ascribed to pneumonia, which presumably is caused by the aspiration of food or secretions in the mouth. From a simple mechanical standpoint, if the child is placed in an extreme Trendelenburg position with the head low, aspiration of infected material into the lung should be relatively impossible regardless of whether a tracheo-esophageal fistula is present or not. I treated one patient with esophageal atresia in this manner, but unfortunately a severe bilateral pneumonia was already present before the child was admitted to the hospital, and death occurred in the usual manner.

24. Plass, E. D.: Congenital Atresia of the Esophagus. *Bull. Johns Hopkins Hosp.* 18:259, 1919.

ANOMALIES OF THE BILIARY TRACT

Congenital defects of the biliary tract are extremely variable. In a series of eighty-nine collected cases Milne²⁵ found that the obliteration occurred in the common bile duct in seventy instances. In thirty-nine cases, the common hepatic duct was also obliterated. In a series collected by Howard and Wolback²⁶ the cystic and hepatic ducts were the most common sites. The largest series encountered in the literature was that of Holmes²⁷ who reviewed over a hundred cases. In the present series of four confirmed cases, all of the extrahepatic ducts were absent. Usually the gallbladder is also absent, but occasionally it may be found as a deformed rudimentary organ. When present it contains mucus but rarely bile. Cirrhosis of the liver with enlargement is present in practically all cases of atresia of the hepatic or common duct. On section, the organ is firm, tough and manifestly fibrosed, and is usually dark green. The spleen is usually enlarged to two or three times its normal size.

Clinically, absence of the gallbladder is not of much importance since few if any symptoms will result from this defect alone. If complete atresia is produced by the absence of a part of the hepatic or common duct, a certain clinical picture is always encountered. One of the first demonstrable signs to be found is jaundice. This usually is noted a day or so after birth, but occasionally may not be discovered, especially by the parents, for ten or twelve days. Little itching is present. The intensity of the jaundice may vary, but the stools are at all times free from bile, as is evidenced by their bulky, grayish-white appearance. Most of the fat ingested is excreted. In a case in the present series, tests were made to determine the amount of fat absorbed, and it was found that 85 per cent of the fat ingested was excreted in the stool. Constipation is frequently present. The urine is heavily loaded with bile pigments. Hemorrhage from mucous surfaces, etc., frequently occurs, but was not encountered in any of the six cases in this series. The duration of life is extremely variable. There are several instances on record in which life was prolonged six or eight months, although the usual length of life is no more than a few weeks.

One of the striking features in this series was the presence of infections, including otitis media, pyelitis, acute bronchitis and pneumonia. Nearly all of the patients under observation suffered from many attacks of such infections; all deaths were caused by one of the four diseases mentioned. There are several conditions that must be

25. Milne, L. S.: Congenital Atresia of the Bile Passages, *Quart. J. Med.* 5: 409, 1911-1913.

26. Howard, C. P., and Wolback, S. B.: Congenital Obliteration of the Bile Ducts, *Arch. Int. Med.* 8:557 (Nov.) 1911.

27. Holmes, J. B.: Congenital Obliteration of the Bile Ducts, *Am. J. Dis. Child.* 11:405 (June) 1916; *Bull. Johns Hopkins Hosp.* 18:75, 1919.

differentiated from congenital atresia of the bile ducts. Familial icterus may be similar, but in this disease the stools contain pigment and the liver is not enlarged. Congenital syphilis may produce jaundice, but if so, other evidences of syphilis should be present. Icterus neonatorum may offer difficulty in the differential diagnosis, but in this instance the jaundice usually appears about the third day of life and disappears about the third week, and the stools contain bile pigment. Few, if any, physical signs of illness are present in icterus neonatorum.

Holmes²⁷ and Ladd²⁸ stated that these anomalies are not hopeless from the standpoint of surgical relief. Holmes noted in the series reviewed by him that "in over 16 per cent of all reported cases of atresia of the bile ducts, both the cystic and hepatic ducts were essentially normal and communicated with each other." In this group it might be expected that the correct surgical procedure (e. g., cholecysto-enterostomy) would offer hope of relief. Of the twenty cases of anomalies (stenosis or atresia) of the bile ducts reported by Ladd, 40 per cent revealed an anatomic situation that theoretically was amenable to surgical intervention. Of the eleven patients operated on, two who had complete atresia of the common duct were relieved of their symptoms and were presumably cured, by cholecystogastrostomy in one instance and by cholecystoduodenostomy in the other. Ladd remarked that up to the date of his report, these were the only instances of survival following operation for atresia of the common duct. In several of the cases reported by Ladd there was merely stenosis of the common duct. Some of the patients survived operation, consisting of dilation of the stenotic area, and were apparently cured.

In none of the cases seen in the clinic of the St. Louis Children's Hospital has operation offered any possibility of relief, since in no instance was an extrahepatic duct present. The shock of the operation is more pronounced in such cases than in normal infants, but not strikingly so except for the tendency to contract infections of various sorts. Of four patients, one was operated on at the age of 7 months by Dr. A. O. Fisher and was alive when last seen, several weeks after operation. No trace of the gallbladder or any of the bile ducts was found at operation. As stated previously, few of these patients attain an age much greater than 6 months.

CONGENITAL DEFECTS OF THE DIAPHRAGM

There can be no doubt that practically all cases of so-called diaphragmatic hernia in newly born infants are in reality instances of congenital defects in the diaphragm. In many cases there is an absence

²⁸ Ladd, W. E.: Congenital Atresia and Stenosis of the Bile Ducts, J. A. M. A. **91**:1082 (Oct. 13) 1928.

of one entire side of the diaphragm. It is difficult to explain why this defect should occur on the left side in from 85 to 90 per cent of the cases unless due to the many openings for various structures passing through the left side of the diaphragm or to the fact that the right side develops first. A peritoneal sac is rarely found in infants. This condition should probably be classified as false hernia, in contrast to true diaphragmatic hernia, which has a peritoneal sac. When the defect consists merely of an opening in the diaphragm, it may occur at almost any of the normal openings, practically all of which, however, are located on the left side. Among children born with the abdominal organs displaced, the mortality is high. In a series of fifty-seven cases collected by Funck-Brentano,²⁹ fifty-one of the patients died within the first twenty-four hours. LeWald³⁰ reported several cases of complete absence of the diaphragm in which the patients lived to adulthood. It seems probable that in these instances the defect existed at birth but that the displacement of the viscera did not occur until later.

Diagnosis.—The symptoms produced by herniation of peritoneal organs through the diaphragm may be extremely varied. In many instances the condition exists for years without symptoms and is discovered accidentally, usually by roentgen examination. On other occasions, severe symptoms are manifested at birth. Patients having symptoms or signs at birth or shortly thereafter practically always represent that group of patients who succumb to the condition early in life.

When symptoms and signs are manifested early after birth, they usually consist of dyspnea (especially of the orthopneic type), cyanosis and vomiting. Occasionally shifting the patient to a certain position will greatly relieve the cyanosis and dyspnea. If the infant survives the initial attack the foregoing symptoms, especially the vomiting, are apt to recur at inconstant intervals throughout life. Examination of the chest reveals evidence of air or gas in the pleural cavity, which in most instances will be mistaken for a pneumothorax until a roentgenogram is taken. Pulmonary sounds may not be heard, but instead, numerous gurgling and rumbling noises are encountered, especially after feeding. The heart is usually displaced to the right. Occasionally practically all the organs of the abdominal cavity including, in order of frequency, the stomach, colon, omentum, spleen and small intestine are found in the thoracic cavity. The vomiting is apparently an evidence of partial obstruction. Constipation is frequently present. Pain may

29. Funck-Brentano: *Hernie diaphragmatique congénitale chez un nouveau-né ayant vécu 65 heures*. Bull. Soc. méd. du dép. de la Seine 3:414, 1900.

30. LeWald, L. T.: *Congenital Absence of the Left Half of the Diaphragm*. Arch. Surg. 14:332 (Jan.) 1927.

be localized in the chest or epigastrium, and when present to a great extent probably is a manifestation of obstruction.

Occasionally, the diagnosis can be made only by fluoroscopic examination following the ingestion of an opaque meal. By this procedure the stomach can be seen to fill in a position above the diaphragm. If the colon is present in the thoracic cavity, a barium sulphate enema will likewise reveal its position above the level of the diaphragm.

Obstruction or strangulation of a portion of the herniated intestine is one of the most frequent complications encountered, and in many instances the diagnosis is not made until this condition necessitates a laparotomy. Of the two cases encountered in the present series, one showed an empyema early in life before admission to the clinic (see report of cases). It was impossible to determine from the history whether the empyema occurred as a complication of pneumonia or whether it was secondary to the presence of intestinal organs in the pleural cavity.

Treatment.—If this defect is so extensive as to be in reality an absence of the left leaf of the diaphragm, operative intervention offers no hope of relief except perhaps to correct any obstruction that might be present. If the defect is small, closure of the opening is possible by surgical means. Careful roentgenologic examination can usually determine to a certain degree the size of the opening, regardless of how much bowel is present in the pleural cavity. The thoracic approach is preferred because of the greater ease of effecting reduction of the herniated mass and because of easier access to the defect in the diaphragm. The difficulties encountered are usually greater than anticipated, regardless of the route chosen. Extreme care must be taken not to perforate any intestinal loops during reduction, because of the poor resistance of the pleural cavity to infection. This same precaution must be taken when the defect is approached through an abdominal incision. Because of the greater amount of difficulty experienced with reduction of the intestinal organs when the abdominal approach is used, greater care must be exercised to prevent tearing of the loops than when the thoracic approach is used. Regardless of whether the abdominal or thoracic incision is chosen, an attempt should be made to tie the last suture in the closure of the pleural cavity during inspiration so as to reduce the degree of pneumothorax. If desired, aspiration of air can be resorted to after closure.

HIRSCHSPRUNG'S DISEASE

The anomaly known as Hirschsprung's disease or congenital megacolon, which no doubt is dependent on a congenital malformation of some kind, can be classified into two types: (1) neurogenic and (2)

mechanical. On some occasions, as described by David,³¹ Brennemann³² and others, a definite stenotic band may be found in the anorectal region just above the sphincter.

Usually, however, no obstructive lesion can be found, and the condition is thought to be due to a defect in the neurogenic mechanism. Perhaps the most logical explanation, as popularized recently by Wade and Royle,³³ is that through overstimulation of the lumbar sympathetic system a peristaltic inhibition of the colon, perhaps accompanied by hypertonicity of the anorectal junction, is produced. Under such physiologic conditions a progressive dilatation of the colon with obstinate constipation would appear to be inevitable. The defect might also be in the nerve endings in the muscular wall or in the ganglion cells. Cameron³⁴ demonstrated a destruction of the ganglion in Auerbach's plexus in a case of Hirschsprung's disease, and offered this pathologic process as the chief etiologic factor.

It has been said by some writers, including Goodman,³⁵ that the unusual length of the descending colon in infancy is a prominent factor in producing obstruction by allowing the intestine to become kinked and doubled up on itself. Anomalies of the mesentery as a cause of the megacolon of Hirschsprung were emphasized by Goebel³⁶ who reported a case with observations at autopsy illustrating the relation between dilatation of the colon and anomalous mesentery.

In spite of the fact that the symptoms presented by the group caused presumably by neurogenic defects and the group caused by an actual anorectal stricture are practically the same, it hardly seems correct to classify the two as a part of the same disease. In a series of twelve cases observed in this clinic, there was no demonstrable obstruction in any except possibly one instance (see report of cases).

Diagnosis.—The condition usually manifests itself within the first few weeks of life. Obstinate constipation and abdominal distention are among the first symptoms and signs encountered. The fecal accumulations or enteroliths may attain tremendous size and become very hard. Vomiting is rarely present. Many of these children will play normally

31. David, V. C.: Congenital Stricture of the Rectum in Children, *S. Clin. North America* 3:1115, 1923.

32. Brennemann, J.: Simple Congenital Anorectal Stricture with Megacolon in Early Infancy, *J. A. M. A.* 89:662 (Aug. 27) 1927.

33. Wade, R. B., and Royle, N. D.: The Operative Treatment of Hirschsprung's Disease: A New Method, *M. J. Australia* 1:137, 1927.

34. Cameron, J. A. M.: On the Etiology of Hirschsprung's Disease, *Arch. Dis. Child.* 3:210, 1928.

35. Goodman, A. L.: Diseases of the Rectum and Anus, in Abt: *Pediatrics*. Philadelphia, W. B. Saunders Company, vol. 3, p. 434.

36. Goebel, F.: Mesenterium commune ileocolicum als Ursache eines Hirschsprungschen Symptomenkomplexes, *Arch. f. Kinderh.* 68:221, 1920.

and maintain practically normal weight and growth. During infancy, many of them will be fretful and cross, and as they become older will complain of severe cramping pains along with abdominal discomfort of a disturbing degree.

In most cases examination reveals pattern formation with peristaltic waves of varying intensity. Seldom is there much tenderness present. A tympanitic note replaces the normal areas of dulness because of the excessive amount of gas present. The abdominal pressure may become so great as to produce edema of the ankles or urinary disturbances. Colonic irrigations and enemas are usually effectual in evacuating large quantities of fecal matter and gas. If no enemas are given, the child may go for days and even weeks without a bowel movement. The fecal discharges are usually offensive.

Roentgenologic examination is helpful and rarely fails to establish or eliminate the diagnosis definitely. As the barium suspension enters the rectum it can be seen to spread rapidly within the greatly dilated lumen of the rectum and slowly spread upward. As stated previously, the dilatation is most often found in the descending colon and sigmoid, but occasionally includes the entire colon and even the distal portion of the ileum. Not infrequently the dilatation will be found to occur in varying positions throughout the colon, creating a fusiform enlargement. In 1 case in the present series, this fusiform dilatation was demonstrated to a marked degree.

Treatment.—It is perhaps fortunate that the greater number of these patients die in early infancy. Medical treatment consisting of mineral oil, daily irrigations and enemas and dietary measures should be tried before surgical intervention is considered. Cathartics are contraindicated because of the inhibitory effect produced on peristalsis after the primary stimulus wears off. All measures should be resorted to, including thorough rectal examination, in an endeavor to locate any obstruction that might be present. If the rectal sphincter is tight, dilation under anesthesia should be carried out.

Dilation of the rectal sphincters was done in two cases, although no definite obstruction could be demonstrated in either. In one child, however, there was a folding of the intestinal wall at a point near the recto-sigmoid junction which apparently produced a partial obstruction. On two or three occasions, when constipation and distention with gas were pronounced, relief was obtained by forcing the finger past this point, which at times felt like a stenosis. Whether there was a real redundancy of colon or merely a slight folding of mucosa could not be determined accurately. This child, who had not had a bowel movement for months, except by the aid of enemas, had a daily voluntary stool for several weeks following dilation. Four months after the dilation he was brought

back by the father, who stated that for two weeks enemas had again been necessary as a routine measure. The sphincter and rectum were again dilated, but sufficient time has not elapsed following the second dilation to determine whether a beneficial effect was again produced. In the second case, in an infant 6 months of age, dilation was followed by improvement in the evacuation of fecal material but not as efficiently as in the first case cited. However, in cases not showing definite stenosis the improvement gained by dilation could be expected to be only temporary. Even if further experience substantiates the moderate improvement obtained in these two instances, no explanation of the mechanism of its production can be offered.

On the basis of their belief that the primary fault lies in the internal sphincter ani, Wade and Royle³³ advised lumbar sympathectomy for Hirschsprung's disease, and reported cases that showed great relief after this operation. This procedure seems to offer the most favorable solution for the treatment of patients with this disease and deserves an extensive trial. Removal of the lumbar sympathetic ganglions on each side is not a serious operation *per se*, and does not involve any of the dangers of peritonitis that accompany the more serious operation of colonic resection. Scott and Morton³⁷ recently reported a case that gave practically a perfect result: Before operation a boy, aged 7, had never had a spontaneous bowel movement, whereas after operation his bowels moved daily without enemas. In 1928, Judd and Adson³⁸ reported two cases in which they operated with favorable results. The technic of the operation is well illustrated in their report.

Resection of the dilated portion of colon yields varying results. Obviously an operation as radical as resection should be resorted to only when the pain, distention, disability, etc., are severe and fail to respond to medical treatment and lumbar sympathectomy. On account of the fecal stasis, any type of resection should be done in two stages, the first operation being limited to either colostomy or anastomosis. In many instances dilatation will occur in the intestine, proximal to the site of resection, with a return of symptoms and signs simulating those existing before resection.

IMPERFORATE ANUS

The formation of imperforate anus is readily explained by the fact that the rectum and anus develop separately, the former being of entodermal and mesodermal, and the latter of ectodermal, origin. The

37. Scott, W. M., and Morton, J. M.: Sympathetic Inhibition of the Large Intestine in Hirschsprung's Disease. *J. Clin. Investigation* 9:13, 1930.

38. Judd, E. S., and Adson, A. W.: Lumbar Sympathetic Ganglionectomy and Ramisectomy for Congenital Idiopathic Dilatation of the Colon, *Ann. Surg.* 88: 479, 1928.

depression at the anal site (proctodeum) which normally develops during the first few months of embryonic life is lined by ectoderm and extends inward to meet the blind end of the entodermal tube, with which it normally connects. Numerous variations of deformities are caused by their failure to fuse (fig. 3). Imperforation occurs once in every 8,000 or 10,000 births. One case was encountered in 6,300 births in the maternity wards of Barnes Hospital during a period of twelve years. Over a similar period of years, however, sixteen patients with this condition were admitted to the St. Louis Children's Hospital. The anomaly is equally common in male and in female infants.

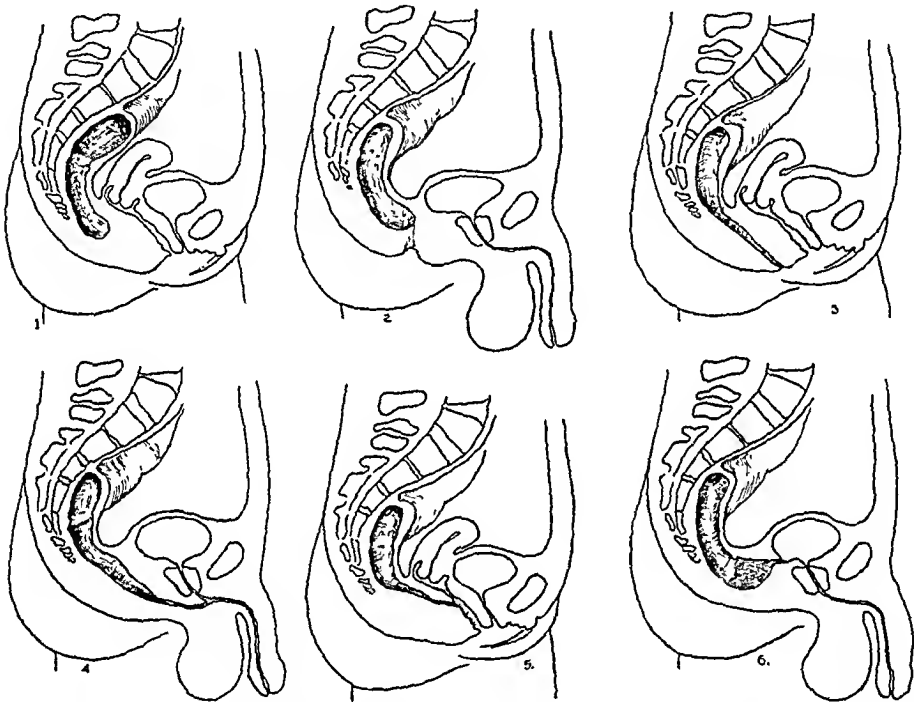


Fig. 3.—Types of imperforate anus and the location of the various fistulous tracts formed: (1) absence of anus (proctodeum); (2) fibrous cord attaching rectal pouch and proctodeum; (3) perineal fistula; (4) urethral fistula; (5) rectovaginal fistula, and (6) rectovesical fistula.

The condition is not difficult to recognize clinically, especially if the anal dimple has failed to form. Usually this dimple is not present. For the first twenty-four hours there may be no symptoms. After the second day distention manifests itself and gradually becomes more marked. The child usually becomes restless after the appearance of distention and occasionally vomits or regurgitates. Muscle spasm over the abdomen is not prominent, although the distention may become so marked as to simulate this phenomenon. The appetite for food usually decreases after the first day until after several days severe dehydration and malnutrition develop. Death is apt to ensue after a week or ten days

unless the condition is corrected surgically or a fistulous tract forms. It is surprising to learn that the small fistulous tracts frequently seen may be compatible with life and good nutrition.

Treatment.—Operative intervention is obviously the procedure of choice. Except in a few instances, as in the presence of a rectovaginal fistula, operation should be performed as soon as the condition is recognized. In most instances all that is necessary is incision of the skin over the sphincter and puncture of the distended rectal pouch which usually presents into the wound. This may be done under local anesthesia, but ether is preferable because of the advisability of dissection of the rectal wall over a distance great enough to allow approximation with the skin. Obviously, if sphincteric control is to be hoped for, incision must be made within the circumference of the sphincter ani muscle. This muscle is practically always present, and effort should be made to find it. Frequently it is so difficult to find the rectal wall and suture it to the skin through the small opening allowed by the sphincter that it is not worth while to attempt this approximation. Unless the approximation is made without tension, the suture will tear through the rectal wall and allow it to retract back to its original position.

Occasionally the rectal pouch ends blindly so high in the pelvis that it cannot be reached through the perineal route as described. After dissection upward for a distance of 2 or 3 cm. has proved futile, it is safer to discontinue the perineal approach and perform a left inguinal colostomy. At the time of performing the colostomy the rectal pouch should be sought. It is usually so widely dilated that if situated high in the pelvis, it can be pushed downward into the floor of the pelvis and be attached there by sutures. This technic allows one to puncture through the sphincter at a later date without much danger of injury to adjacent organs. This procedure was carried out successfully in a case at the St. Louis City Hospital.

Wangensteen and Rice³⁹ suggested a simple method for determining the method of approach, perineal or abdominal, in operations for imperforate anus. They take a roentgenogram of the abdomen with the child held head downward, to determine the position of the rectal gas. Inversion of the infant with head down allows the gas to seek the position nearest the sphincter ani muscle. The distance intervening between the gas and anal dimple determines what procedure to adopt. If the gas shadow is close to the skin the perineal route is indicated.

When a fistulous tract to the exterior surface is present, operative correction of the deformities may be postponed for some time, depending on the size of the sinus tract. If a rectovesical fistula is present.

39. Wangenstein, D. H., and Rice, C. D.: Imperforate Anus: A Method of Determining the Surgical Approach. *Ann. Surg.* 92:77, 1930.

an attempt should be made to divert the fecal stream from the bladder as soon as possible, on account of the possibility of renal infection. The presence of the fistula in the perineal region probably indicates the type most readily cured. At the time that the opening is made in the rectal pouch through the sphincter ani muscle, the perineal fistula should be closed. Closure of the fistula by a deep stay suture threaded over a button on each side of the fistula, at least 2 cm. from the opening of the fistula, is perhaps to be preferred to the method of closure by purse-string sutures or a similar method on account of the tendency for the sutures to cut through the tissues. If it becomes necessary to perform a colostomy, nearly any type of small fistula will close spontaneously. It is much more difficult to obtain closure of these fistulas after the normal opening through the sphincter ani muscle is established, on account of the small size of the opening. It may be necessary to resort to more than one attempt at closure of the large fistulas that are frequently seen opening into the vagina, but several attempts should be made before one admits failure. Mobilization of the rectum by an incision over the sacral region has been advised on numerous occasions, but is a radical procedure and no doubt carries a high mortality with the operation. The result is apt to be satisfactory, however, if the infant survives, because of the ability to get the rectal wall down through the sphincter.

The results of operations for correction of imperforate anus are somewhat discouraging. The mortality from operation is quoted at 25 per cent. Of the sixteen patients admitted to the St. Louis Children's Hospital, all of whom were operated on there or elsewhere, three died; this constitutes a mortality of about 18 per cent. Formation of stricture at the site of the newly created anus is frequently encountered. Another complication to be feared is fecal incontinence, which occurs on numerous occasions.

REPORT OF CASES

Malformation of Intestine.—Twelve cases of malformation of the duodenum were encountered, all of which presented obstructive symptoms. Four of these consisted of a stenosis of the loop, usually in the second part, and in children whose ages varied between $1\frac{1}{2}$ and 8 weeks. Gastro-enterostomy was performed on all patients, three of whom survived and were free from symptoms when discharged. One died twenty-four hours after operation. The youngest of the three infants that survived was $1\frac{1}{2}$ weeks of age. The obstruction in this instance may have been complete, but it scarcely seems probable that the infant would have lived that long in the presence of complete obstruction without more dehydration, etc. The obstruction in the other two infants with stenosis that survived was no doubt only partial, since one was 6 weeks

and the other 8 weeks of age at the time of operation. In four cases there was obstruction due to fibrous bands, all of which were located in the terminal portion at the ligament of Treitz. The ages of these patients were 7 years, 3 weeks, 3 days and 4 days, respectively. Laparotomy was performed and the bands were cut, but all died. The obstruction was apparently complete in the latter two cases. One of these was rather remarkable, because the band accompanied the superior mesenteric artery. The band was severed, but the artery was so short that obstruc-

Congenital Malformations of the Intestine and Bile Ducts in Eighty-One Cases

	No. of Patients		Anomaly	No. of Instances
	Male	Female		
Malformation of the esophagus..	1	3	Stenosis only.....	1
			Atresia with tracheal fistula.....	2
			Atresia without tracheal fistula.....	1
Malformation of the pylorus.....	..	1		
Malformation of the duodenum..	5	7	Incomplete rotation.....	3
			Obstruction by adhesive bands.....	4
			Stenosis.....	4
			Atresia with blind loop.....	1
Malformation of the jejunum....	1			
Malformation of the ileum.....	6	3	Complete atresia at lower ileum.....	4
				(1 multiple)
			Adhesive band in ileocecal region.....	4
			Obstruction by imperforate diaphragm...	1
Malformation of the colon.....	1	1	Hole in transverse colon (congenital origin).....	1
			Absence of mesentery.....	1
Meckel's diverticulum.....	5	..	Stenosis of ileum.....	1
			Huge cystic mass.....	1
			Perforation with peritonitis.....	1
			Found at autopsy; no symptoms.....	2
Anomaly of the bile ducts.....	5	1		
Imperforate anus.....	8	8	Females (8):	
			Rectovaginal fistula.....	6
			Perineal fistula.....	2
			Males (8):	
			Rectovesical fistula.....	1
			Perineal fistula.....	2
			No fistula.....	5
Transposition of the viscera.....	6	3		
Hirschsprung's disease.....	11	1		
Absence of the diaphragm.....	..	2		
Eversion of the diaphragm....	2			
	51	30		

tion was obviously still present. However, it was possible to stretch the artery without difficulty, to a degree that eliminated all obstruction. Robinson,⁴⁰ Slocumb⁴¹ and others have emphasized the production of gastric dilatation, especially after operations, by pressure of the

40. Robinson, B.: Dilatation of the Stomach from Pressure of the Superior Mesenteric Artery, Vein and Nerve on the Transverse Segment of the Duodenum, Cincinnati Lancet Clin. 45:577, 1900; quoted by Slocumb (footnote 41).

41. Slocumb, L. H.: Compression of the Duodenum by the Mesentery and Superior Mesenteric Vessels: An Underlying Cause of Gastric Dilatation, Surg., Gynec. & Obst. 44:359, 1927.

mesenteric vessels on the duodenum. The obstruction in three of the twelve cases was caused by incomplete rotation of the intestine with only partial obstruction. In one case the duodenum was anterior to the colon; in another the duodenum had a long mesentery that passed downward instead of to the left. In the third case a volvulus of congenital origin was found. Nothing surgical could be done in either of these cases. The first patient died, but the other two lived. In the entire group of duodenal anomalies there was only one case (in a patient aged 2 days when seen) of complete atresia with a blind loop. A duodenojejunostomy was performed, but the child died two days later. It is remarkable that all of the patients with a definitely complete obstruction died within a short time after operation. Shock appeared to be the primary cause of death.

In one instance a stenosis of the pylorus with incomplete obstruction was encountered in an infant, 4 weeks of age. The stenosed area was short and was repaired by the Mikulicz technic. The child survived the operation and was well at the time of discharge.

Only on one occasion was the jejunum the site of malformation in the present series. This infant had a complete atresia a few centimeters beyond the ligament of Treitz. An end-to-side anastomosis was performed under local anesthesia, but the child died twenty-four hours after operation.

Of the nine patients with obstruction of the ileum, four had complete atresia. The length of the defect caused by the atresia varied between 2 and 10 cm. In one of these cases the atresia was multiple, occurring in several places in the distal half of the ileum. The age of these infants on the day of admission and operation varied from 2 to 4 days. Intestinal anastomosis was performed on two of them and ileostomy on the other two. All died within twenty-four hours after operation. On four occasions obstruction was found to be caused by fibrous bands constricting the ileum a few centimeters from its junction with the cecum. In an infant, aged 3 days, this fibrous band communicated with a cyst several centimeters in diameter, containing clear straw-colored fluid; this was considered a cystic dilatation of a remnant of the vitelline duct. The infant survived the operation, but died three weeks later following a second operation for intestinal obstruction of acquired etiology. The other three infants in this group were from 1½ to 4 weeks of age, but had had symptoms for three or four days. In one infant it was found that after the constricting bands were severed, the constriction was so prominent as to require surgical correction. A repair of the Heineke-Mikulicz type was performed. The infant lived and was discharged well. The ninth case in this series of lesions of the ileum constituted the only one in which an obstruction was caused by a diaphragm. This diaphragm was located in the terminal ileum a few

centimeters from the ileocecal junction. The colon, however, was no larger than a lead pencil and barely admitted a probe at autopsy the day following operation.

Meckel's diverticula were observed in only five infants and in two instances the defect was not discovered until after death, which was caused by diseases not related to the anomaly. In an infant, 13 days of age, with symptoms of partial obstruction for six days, the diverticulum caused a stenosis of the ileum at its point of attachment. An ileostomy was performed, but the infant died on the fifth post-operative day. On another occasion, there were no symptoms, but a large firm cystic mass had been present since birth eight weeks previously. Owing to deep attachments, the cyst was marsupialized, but the child died two days later, presumably of peritonitis. In the fifth case a child, $2\frac{1}{2}$ years of age, had abdominal pain and vomiting for twenty-four hours. Laparotomy revealed peritonitis caused by perforation of the base of a Meckel's diverticulum which was attached to the ileum near the midportion. The child died of peritonitis and bronchopneumonia five days after operation.

Lesions of congenital origin were encountered in the colon in only two instances, except for the case previously mentioned, in which a diaphragm in the lumen of the terminal ileum was found with a generalized stenosis of the entire colon. In one of these cases, in an infant 2 days of age at the time of death, a large defect 2 or 3 cm. in diameter was found at autopsy in the transverse colon, through which considerable meconium had escaped into the peritoneal cavity. Because of such obscure and indefinite symptoms, including lack of vomiting, this infant was not operated on. Another infant, 2 days of age, with abdominal symptoms since birth, was operated on and found to have gangrene of 3 inches (7.6 cm.) of the transverse colon, caused by lack of attachment of the mesentery at this point. The gangrenous portion was resected and an anastomosis performed, but the child died two days after operation.

Malformations of the Esophagus.—This condition was encountered in four infants in the present series. On one occasion the obstruction was not complete, consisting merely of a stenosis in the terminal end of the esophagus. This child was 3 years of age when last seen and was able to swallow soft foods if dilation was performed at frequent intervals. Another infant, 5 months of age, had had a gastrostomy performed elsewhere on the fourth day of life because of an atresia opposite the fifth dorsal vertebra. The two remaining patients, aged 5 and 6 days, respectively, had regurgitated all food since birth and had practically all the symptoms of atresia of the esophagus with a tracheo-esophageal fistula. Each was cyanotic and had frank bilateral pneumonia when

admitted. Although there was little hope for them on account of their moribund condition, a gastrostomy was performed on each. Death ensued from twenty-four to forty-eight hours after operation. As mentioned previously, a jejunostomy is probably preferable to gastrostomy because of possible regurgitation. The anomaly in each of these cases was similar to type 1 in figure 2.

Anomalies of the Biliary Passages.—Of the six cases of this condition occurring in this series two were not confirmed by operation or autopsy, but the history of jaundice and white stools since birth makes the diagnosis of congenital malformation of the bile ducts most probable. One infant was 10 weeks of age and in fairly good physical condition at the time of discharge, except for enlargement of the liver and the spleen. The other one, 10 months of age, was moribund at the time of discharge. Operative or postmortem confirmation was obtained in four patients whose ages varied between 3 weeks and 7 months. In none of the four cases were remnants of any of the extrahepatic bile ducts found. On one occasion a rudimentary abnormal gallbladder without a cystic duct attached was found. All showed large greenish livers with varying degrees of cirrhosis. In three of the four patients the spleen was enlarged to two or three times its normal size. One of the infants, aged 7 months, who was operated on, was alive when last seen four weeks after operation. The other two died a few weeks after operation. In none of the patients on whom operation was performed was it possible to carry out any surgical procedure that would offer relief.

Hirschsprung's Disease.—There were twelve cases of megacolon in the present series, but in two of these the diagnosis was questionable. The ages varied between 5 weeks and 12 years, with an average of 3.8 years. It is significant that all the patients except one were males. The fact that the age of each of the four patients who died was less than 1 year supports the statement made by different authorities that if the child suffering from Hirschsprung's disease survives the first year of life, he is apt to live for many years. In all except three cases, symptoms had been present since birth. Organic obstruction was not found in any of the cases. Dilation of the rectum and sphincter was performed in two cases even though a definite obstruction or stenosis could not be demonstrated. Moderate improvement followed the dilation, especially in one case.

Congenital Defects in the Diaphragm.—In the two cases observed in this series the defect in the diaphragm occurred on the left side, as is usually the case, and measured 2 by 3 cm. in one instance and 2 by 7 cm. in the other. One of the patients had undergone a thoracostomy for empyema before entry to the St. Louis Children's Hospital, and had apparently completely recovered. Both of these patients were so acutely

ill on admission to the hospital that consideration of any surgical procedure was out of the question. They died shortly after admission. Autopsy on one patient, 6 years of age, revealed a herniation of the colon and stomach through a defect 2 by 3 cm. in size on the left side of the diaphragm, with strangulation of both organs and early gangrene of the stomach. Postmortem examination of the other infant, aged 1 year, revealed the fact that practically all the abdominal organs except the liver, duodenum and sigmoid had passed through a defect in the diaphragm, about 2 by 7 cm. in size, into the thoracic cavity. The embarrassment of the heart by pressure of these organs contributed to the child's death, since obstruction was apparently not a prominent factor in this instance.

Eventration of the Diaphragm.—Two cases of eventration, with high displacement of the diaphragm on the left side, were observed in the present series and were reported by Clopton⁴² in detail. One child, 2 years of age, had been operated on previously for empyema, but returned for treatment for an abscess of the wall of the chest. The empyema had been preceded by the development of influenza and bronchopneumonia a few days before. When first seen, the condition was regarded as a hernia through a defect in the diaphragm. It was not until after a careful study of a series of roentgenograms, including those taken before the thoracostomy for empyema, that the condition was found to be an eventration and not a defect of the diaphragm. The child improved slowly and was discharged well. In the second case of eventration, a child, 6 years of age, was admitted to the hospital because of malnutrition. On examination, the heart was found on the right side, and a tympanic percussion note was found to extend up on the chest as far as the third rib on the left side. The liver was displaced downward on the right side as far as the crest of the ileum. The child improved satisfactorily while in the hospital and was symptomless at the time of discharge.

Transposition of the Viscera.—This anomaly may be limited to thoracic organs, but in eight of the nine cases observed in which transposition of any organs was detected, there was transposition of the abdominal viscera. In four of the nine cases roentgen examination showed transposition of the heart, liver, stomach, cecum and sigmoid. In four other cases the roentgen shadows of the heart and liver were in reversed position. The position of the organs of the intestinal tract in this group is not definitely known, since roentgen examination of the gastrointestinal tract was not carried out. In all probability, however, the position of the intestinal viscera was also reversed. In one of the nine cases the heart was transposed to the right side, but the only

42. Clopton, M. B.: Eventration of the Diaphragm, *Ann. Surg.* 23:154, 1923.

change in the position of the abdominal organs was a slight displacement. The chief complaints of practically all the patients in this series of nine cases were weakness, anorexia and lack of energy since birth. All were malnourished. In addition to the foregoing symptoms and signs, there had been cyanosis since birth in two cases. The ages of the patients in this group varied between 1 month and 6 years, averaging 4 years. One died in the hospital with pertussis and pneumonia. Another infant, aged 1½ years, died as a result of cardiac decompensation. All viscera were transposed and the spleen was absent.

Imperforate Anus.—Of the sixteen patients with imperforate anus admitted to the hospital, eight were males and eight females. The ages varied from 1 day to 11 years, with the average about 1.3 years. Of the eight girls, six had a rectovaginal fistula, and two a perineal fistula. Of the eight boys, one had a vesical fistula, two a perineal fistula and five no fistula. Four of this group of five patients were very young and had had an opening made at the site of the anus within a day or two after birth; the fifth child was 11 years of age and had undergone the primary operation at the age of 4 days, and two operations a few years before the present admission for correction of a stricture. At the time of admission he had partial fecal incontinence. It has been impossible to conduct observations for a great length of time on any of the patients except in the instance mentioned. However, the results in the patients who were observed at intervals were, on the whole, discouraging. There was a strong tendency toward the formation of a stricture of the anus after the simple procedure of making an opening through the anal dimple. This tendency was even more pronounced when a fistula was present before the opening was made through the sphincteric muscle. Colostomy had not been a necessary procedure on any of these patients previous to admission, and on only one occasion, when the distance between the rectal pouch and the proctodeum was too great, was colostomy performed in the St. Louis Children's Hospital. This child, 1 day of age, died the next day. In this series of ten cases there were two other deaths, each following an operation, one of which was performed elsewhere. In this case a severe secondary hemorrhage followed the operation, before the patient's admission to the Children's Hospital.

EXPERIMENTAL SHOCK

XI. A STUDY OF THE ALTERATIONS IN THE VOLUME OF BLOOD AND IN THE WATER CONTENT OF BLOOD AND OF MUSCLE THAT ARE PRODUCED BY HISTAMINE *

VIRGINIA BUTLER, M.S.

J. W. BEARD, M.D.

AND

ALFRED BLALOCK, M.D.

NASHVILLE, TENN.

The possibility that histamine is the cause of "shock" after trauma has been extensively speculated on in recent years. Keith¹ and others have found that severe injuries are followed by a diminution of the volume of blood. Harris and one of us (Dr. Blalock)² found that trauma to the muscles and to the intestines and burns are associated with a decrease in the water in the blood and in the muscles other than those at the sites of the injuries. The study indicated that the loss of fluid from the blood stream into and from the traumatized areas was responsible for the concentration of the blood. It is known that histamine causes an increase in the concentration of the blood. Since histamine causes a general dilatation of capillaries and possibly an increase in their permeability, it was believed that histamine would probably cause a general loss of fluid from the blood stream instead of a local loss into the traumatized area as was found after trauma, and that an increase in the water content of all of the muscles of the body would be found. It was for the purpose of determining this point that these studies were begun.

The studies included determinations of the volume of blood and of plasma, the red blood cell count, the hemoglobin, the chloride content and the water content of the blood and muscles.

METHOD

All of the experiments were performed on dogs. Most of these were anesthetized by sodium barbital administered intravenously (0.3 Gm. per kilogram of body weight). The same anesthetic in identical amounts had been employed in

* Submitted for publication, Jan. 27, 1931.

* From the Departments of Physiology and Surgery of Vanderbilt University.

1. Keith, N. M.: Report of Shock Committee, London Medical Research Committee, 1919, no. 27.

2. Harris, P. N., and Blalock, A.: Experimental Shock: X. Observations on the Water Content of the Tissues of the Body After Trauma and After Hemorrhage, *Arch. Surg.* 22:638 (April) 1931.

the previous experiments by Harris and Blalock² on the effects of trauma. In the remaining experiments, morphine sulphate was used as the anesthetic. The arterial blood pressure was determined by placing in the carotid artery a cannula connected to a mercury manometer.

The dye method for determining the volume of the plasma and the blood that was introduced by Keith, Rowntree and Geraghty³ was employed as described by Rowntree, Brown and Roth⁴ in their recent book. The hemoglobin was determined by the Newcomer method⁵ with a Bausch and Lomb hemoglobinometer. The chlorides were determined by the method of Whitehorn.⁶

The water content of blood and muscle was determined on samples obtained before histamine was injected into the subcutaneous tissues and after the blood pressure had been maintained at a low level for at least several hours by repeated injections. The blood was withdrawn from the femoral vein. Tissue was obtained from the pectoral muscle and one of the flexor muscles of the thigh at the beginning of the experiments and from symmetrical sites on the opposite side of the body at the end of the experiments. The muscle usually varied in weight from 1 to 2 Gm. The specimens were placed in small beakers of known weight, and the muscle was cut into small pieces in order to facilitate drying. After the beaker containing the blood or muscle was weighed, it was placed for forty-eight hours in an oven, the temperature of which was kept at as nearly 105 C. as possible. At the end of this time, it was again weighed, and the content of the tissues in water and solids was determined.

For purposes of comparison, the effects of the removal of whole blood and of blood plasma were studied. These experiments were of approximately the same duration as those in which histamine was injected. Harris and one of us (A. B.)² had previously determined the effects of hemorrhage and of the removal of plasma on the water content of blood and muscle. In the present experiments, the volume of blood and of plasma, the red blood cell count, the hemoglobin and the chloride content were determined before and after a low blood pressure had been produced by the removal of whole blood or of plasma. In the experiments in which the effects of hemorrhage were studied, whole blood equaling 1 per cent of the body weight was removed at one hour intervals until a low blood pressure resulted. In the experiments in which the effects of the removal of blood plasma were studied, whole blood equaling 1 per cent of the body weight was removed at one hour intervals, the blood was defibrinated and centrifugated, and the red blood cells plus enough plasma to equal one half of the volume of blood which had been removed were reintroduced.

RESULTS

In the four experiments in which the effect of the subcutaneous injection of histamine on the volume of blood was studied, a reduction in volume was found. This was associated with an increase in the red blood cells and hemoglobin and either no change or a slight reduc-

3. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**:547 (Oct.) 1915.

4. Rowntree; Brown, and Roth: *The Volume of the Blood and Plasma*, Mayo Clinic Monographs, Philadelphia, W. B. Saunders Company, 1929.

5. Newcomer, H. S.: *J. Biol. Chem.* **37**:465, 1919.

6. Whitehorn, J. C.: A System of Blood Analysis, *J. Biol. Chem.* **45**:449, 1920.

tion in the chloride content. The reduction in the volume of blood consisted, in the main, of a diminution in the volume of plasma. The results of these experiments are given in table 1.

Whole blood which equaled 1 per cent of the body weight was removed at one hour intervals in three experiments until a low blood pressure resulted. The reduction in the volume of blood was associated

TABLE 1.—*The Effects of Histamine*

Ex- peri- ment	Weight of Dog, Kg.	Total Amount of Hista- mine, Mg.	Time of Determi- nations	Mean Blood Pressure, Mm. of Hg	Hemo- globin, per Cent	Red Blood Cell Count	Volume of Plasma, Cc.	Volume of Blood, Cc.	Blood Chloride Content, Mg. per 100 Cc.
1	11.31	70	Control period...	120	110	9,040,000	568	1,159	525
			4 hours after ini- tial histamine....	58	118	10,400,000	472	1,006	531
2	16.45	35	Control period...	112	105	8,020,000	1,058	2,074	548
			1½ hrs. after ini- tial histamine....	26	115	9,900,000	664	1,580	535
3	9.51	45	Control period...	140	90	8,940,000	472	881	545
			3½ hrs. after ini- tial histamine....	56	102	10,200,000	345	683	495
4	10.73	128	Control period...	130	87	8,200,000	442	797	540
			3¾ hrs. after ini- tial histamine....	68	100	9,520,000	331	691	472

TABLE 2.—*The Effects of the Removal of Whole Blood at One Hour Intervals*

Ex- peri- ment	Time of Determi- nations	Weight of Dog, Kg.	Mean Blood Pressure, Mm. of Hg	Hemo- globin, per Cent	Red Blood Cell Count	Plasma Volume, Cc.	Blood Volume, Cc.	Blood Chloride Con- tent, Mg. per 100 Cc.	Total Amount Bled in per Cent of Body Weight
1	Control period... 4½ hrs. after ini- tial bleeding.....	20.4	110	85	7,950,000	1,092	1,796	508	5
		18.93	60	75	6,020,000	654	1,011	538	
2	Control period... 3½ hrs. after ini- tial bleeding.....	18.85	115	80	6,850,000	981	1,721	503	4
		17.9	70	72	6,270,000	637	1,069	521	
3	Control period... 4½ hrs. after ini- tial bleeding.....	16.6	120	92	7,810,000	831	1,662	487	5
		15.5	58	85	6,310,000	585	940	520	

with a greater proportional diminution in the volume of red blood cells than of plasma. The red blood cells diminished, the percentage of hemoglobin decreased, and the chloride content increased slightly. The results of these experiments are given in table 2.

Blood plasma which equaled 0.5 per cent of the body weight was removed at one hour intervals in five experiments until the blood pressure definitely declined. The level of the mean blood pressure was not as low in these experiments as in the others, since additional bleeding sufficient to allow the removal of the usual amount of plasma

would have resulted in the death of the animal. The diminution in the volume of blood was accounted for almost entirely by the reduction in the volume of plasma. The red blood cell count increased, the percentage of hemoglobin increased and the chloride content usually decreased slightly. The results of these experiments are given in table 3.

The effects of the subcutaneous injection of histamine on the water content of blood and muscle was determined in experiments on nine dogs. Six of these were anesthetized by morphine and the remaining three by barbital. The results were the same with the two types of anesthetics. The time that elapsed between the initial injection of his-

TABLE 3.—*The Effects of the Removal of Blood Plasma at One Hour Intervals*

Ex- per- iment	Time of Determin- ations	Weight of Dog, Kg.	Mean Blood Pressure, mm. of Hg	Hemo- globin, per Cent	Red Blood Cell Count	Plasma Volume, Cc.	Blood Volume, Cc.	Blood Chloride Con- tent, Mg. per 100 Cc.	Total Amount Removed in per Cent of Body Weight
1	Control period...	13.6	115	90	7,800,000	703	1,143	545	
	5½ hrs. after ini- tial removal.....	13.0	100	110	9,000,000	459	871	495	3.0
2	Control period...	11.88	115	85	6,900,000	584	942	569	
	5 hrs. after ini- tial removal.....	11.32	100	100	9,660,000	347	694	548	2.75
3	Control period...	19.4	125	95	7,140,000	1,056	1,600	512	
	5 hrs. after ini- tial removal.....	18.9	96	108	8,710,000	579	1,179	490	2.75
4	Control period...	16.57	130	100	8,670,000	793	1,474	483	
	5½ hrs. after ini- tial removal.....	15.72	90	118	10,020,000	483	1,181	446	3.0
5	Control period...	7.67	98	87	9,270,000	319	632	515	
	4½ hrs. after ini- tial removal.....	7.33	60	90	202	449	528	2.25

tamine and the completion of the experiment varied from four hours and fifteen minutes to seven hours and twenty minutes. The mean blood pressure at the time the second samples were obtained varied from 14 to 52 mm. of mercury. The total amount of histamine that was injected in the different experiments varied from 15 to 80 mg. The water in the blood was decreased. The average control water content of the blood in the nine experiments was 80.79 per cent, and the average content at the completion of the experiments was 77.31 per cent. In seventeen of the eighteen analyses, the water content of the muscle was lower at the end than at the beginning of the experiments. The average content in water of the pectoral muscle was 75.53 per cent at the beginning of the experiments and 74.22 per cent at the end. For the thigh muscle, the average water content at the beginning of the experiments was 75.31 per cent and at the end,

73.84 per cent. The alterations produced were practically identical with those found by Harris and Blalock² in studying the effects of the removal of blood plasma and the effects of intestinal trauma, trauma to the legs and burns. However, the latter experiments presented the additional fact that injury causes an increase in the water content of the traumatized tissues. The results of the experiments on histamine are given in table 4.

TABLE 4.—*The Effects of the Subcutaneous Injection of Histamine on the Water Content of Blood and Muscle*

Ex- peri- ment	Time of Observation	Weight of Dog, Kg.	Mean Blood Pressure, Mm. of Hg	Water Content of Blood, per Cent	Water Content of Pectoral Muscle, per Cent	Water Content of Flexor Muscle of Thigh, per Cent	Total Amount of Hista- mine, Mg.	Type of Anes- thetic
1	Control period.....	128	81.85	72.55	73.8	80	Morphine
	7¼ hours after initial histamine.....	44	72.80	70.65	72.6		
2	Control period.....	105	82.0	76.85	75.0	45	Morphine
	6¾ hours after initial histamine.....	30	78.4	73.20	72.2		
3	Control period.....	117	78.65	73.21	72.45	15	Morphine
	3¾ hours after initial histamine.....	52	74.95	73.10	74.60		
4	Control period.....	118	81.02	75.78	76.48	70	Morphine
	7¼ hours after initial histamine.....	40	80.03	74.35	73.80		
5	Control period.....	128	77.30	73.91	74.75	70	Morphine
	4¼ hours after initial histamine.....	35	73.80	73.60	73.68		
6	Control period.....	120	77.61	74.00	74.12	40	Morphine
	7 hours after initial histamine.....	34	74.82	72.00	72.55		
7	Control period.....	12.92	134	82.38	78.87	76.85	40	Barbital
	7¼ hours after initial histamine.....	12.77	40	78.00	77.65	75.95		
8	Control period.....	11.55	104	83.15	76.8	75.68	25	Barbital
	7 hours after initial histamine.....	11.22	14	80.20	75.62	72.62		
9	Control period.....	13.94	130	83.12	78.30	78.62	15	Barbital
	6¼ hours after initial histamine.....	13.82	50	82.82	76.87	76.60		

COMMENT

The alterations in the volume of blood and of plasma, the red blood cell count, the hemoglobin and the chloride content produced by the subcutaneous injection of histamine and by the removal of blood plasma were similar. The removal of whole blood produced different changes. In the experiments in which histamine was injected, 80 per cent of the decrease in the volume of blood was due to the loss of plasma; in the experiments in which blood plasma was removed, it was 90 per cent, and in the experiments in which whole blood was removed it was 50 per cent. The similarity in the effects that are produced by

histamine and by the removal of plasma suggest that histamine causes the loss of plasma through the walls of the capillaries. As has been stated previously, trauma to muscle and to the intestines and burns result in a loss of fluid from the blood stream into the injured area, and this is probably responsible for the concentration of the blood. The water content of the striated muscle elsewhere was decreased. In view of these observations, we believed before determining the water content of the muscles before and after injecting histamine that the drug would cause an increase in the water content of all of the muscles of the body, since its effect is general and since no trauma was inflicted to any part of the body. In this we were mistaken, and it is important to note that we found the water content of both blood and muscles decreased.

We are unable to state, from the present experiments, whether or not the content in water of all of the tissues of the body is decreased by histamine as determinations were performed only on blood and muscle. It is difficult to perform such studies on the intra-abdominal and intrathoracic organs since the taking of the control samples requires a major operation which may alter the subsequent determinations. Experiments in which the results in a series of normal dogs are compared with those in which such procedures as the injection of histamine have been carried out are unsatisfactory because the water content of the tissues varies in different animals.² Striated muscle is easily obtainable, and it takes up and releases water readily. Volkmann⁷ stated that 50.8 per cent of the total water of the body tissues is in muscle. In animals deprived of water Durig⁸ found that muscle lost the greatest weight. In experimental diarrhea, Tobler⁹ found that 65 per cent of the loss in weight was by muscles. Marriott¹⁰ states: "The body possesses an available store of water which exists for the greater part in the muscles and in the skin, and which can be drawn upon to some extent before any considerable degree of desiccation of other parts of the body occurs." Analyses on skin are unsatisfactory because it is impossible to be sure that all of the fat has been removed from its under surface.

As has been stated previously, histamine causes a loss of fluid from the blood stream and from striated muscle. Some of this is lost in

7. Volkmann, A. W., quoted by Engels, W.: *Arch. f. exper. Path. u. Pharmacol.* **51**:346, 1904.

8. Durig, A.: *Wassergehalt und Organfunction*, *Arch. f. d. ges. Physiol.* **85**:401, 1901.

9. Tobler, L.: *Zur Kenntnis des Chemismus akuter Gewichtstürze*, *Arch. f. exper. Path. u. Pharmacol.* **62**:431, 1910.

10. Marriott, W. McKim: *Anhydremia*, *Physiol. Rev.* **3**:275, 1923.

the expired air and urine. Large amounts of histamine administered intravenously are usually accompanied by immediate diarrhea, and it is possible that histamine causes an increase in the passage of fluid into the lumen of the intestines. In the present experiments, analyses were performed to determine the water content of only blood and striated muscle, and it is not possible to state whether or not the water content of other tissues in the body was altered. It is interesting that histamine is accompanied by the same type of alteration in the water content of blood and muscle as is found after trauma and after burns.

SUMMARY

The volume of blood and of plasma, the red blood cell count, the hemoglobin and the chloride content were determined before and after a low blood pressure had been produced by the subcutaneous injection of histamine, by the removal of blood plasma and by the removal of whole blood. The injection of histamine produced alterations that were similar to those which accompanied the removal of blood plasma.

The injection of histamine caused a decrease in the water content of striated muscle. The alterations were similar to those produced by trauma, by burns and by the removal of blood plasma.

EXPERIMENTAL SHOCK

XII. A STUDY OF THE EFFECTS OF HEMORRHAGE, OF TRAUMA TO MUSCLES, OF TRAUMA TO THE INTESTINES, OF BURNS AND OF HISTAMINE ON THE CARDIAC OUTPUT AND ON BLOOD PRESSURE OF DOGS *

G. S. JOHNSON, M.D.

AND

ALFRED BLALOCK, M.D.

NASHVILLE, TENN.

In a previous study by one of us (Dr. Blalock¹) the effects of graded hemorrhages on the cardiac output and blood pressure were determined. In experiments on dogs anesthetized with morphine it was found that the repeated removal of blood is usually associated with a decline in the cardiac output from 30 to 50 per cent below the normal level before a marked diminution in the mean blood pressure occurs. In subsequent experiments² it was found that the loss of blood into the injured area after trauma to an extremity was instituted was sufficient to account for the decline in the blood pressure. Mild trauma to an extremity,³ trauma to the intestines³ and burns³ were studied, and the results indicated that the loss of plasma into the injured area was the chief if not the sole cause of the sustained low blood pressure that resulted. Evidence indicating that the decline in blood pressure in these experiments was due to a histamine-like substance was not found. It was believed that additional evidence as to the initiating agent in shock might be obtained from comparative studies on the effects of hemorrhage, of trauma and of histamine on the cardiac output and blood pressure. It was for this purpose that these studies were performed.

METHODS AND RESULTS

Dogs were used in all the experiments. Sodium barbital (0.3 Gm. per kilogram of body weight administered intravenously) was employed

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* From the Department of Surgery, Vanderbilt University.

1. Blalock, Alfred: Mechanism and Treatment of Experimental Shock: I. Shock Following Hemorrhage, *Arch. Surg.* **15**:762 (Nov.) 1927.

2. Blalock, Alfred: Experimental Shock: The Cause of the Low Blood Pressure Produced by Muscle Injury in Dogs, *Arch. Surg.* **20**:959 (June) 1930.

3. Blalock, Alfred: Experimental Shock: VI. The Probable Cause for the Reduction in the Blood Pressure Following Mild Trauma to an Extremity, *Arch. Surg.* **22**:598 (April) 1931; VII. The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns, *ibid.* **22**:610 (April) 1931; VIII. The Composition of the Fluid that Escapes from the Blood Stream After Mild Trauma to an Extremity, *ibid.* **22**:617 (April) 1931.

as the anesthetic in most of the experiments, but in at least one experiment in each of the various groups to be described, morphine sulphate was used. The results were approximately the same with the two types of anesthetics. Sodium barbital was preferable in that it produced deeper narcosis, while morphine anesthesia was supplemented by ether while the trauma was being instituted. Sodium barbital anesthesia was undesirable in that it alone produced a rather marked acceleration of the pulse rate and a lessening of the pulse pressure. Since more experiments were performed under barbital anesthesia than under morphine and since the advantages of its use seemed to outweigh the disadvantages, only the experiments that were performed with barbital as the anesthetic will be described in detail in this paper.

The blood pressure was determined by placing in either the carotid or the femoral artery a cannula connected to a mercury manometer. Valves were employed for the determination of the maximum and minimum pressures. The consumption of oxygen was determined with the Benedict spirometer, the Roth graphic recording device being used. Samples of blood were withdrawn under oil from the right ventricle and femoral artery, and analyzed for their oxygen content in the Van Slyke-Neill manometric blood apparatus. The cardiac output was calculated by the Fick formula:

$$\frac{\text{Cc. of oxygen consumed per minute}}{\text{Cc. of oxygen taken up by 1 cc. of blood in passing through the lungs}} = \frac{\text{Cc. of blood passing through the lungs per minute}}{\text{Cc. of blood passing through the lungs per minute}}$$

The blood that was withdrawn for analyses was replaced by blood obtained from another dog. The pulse rate and temperature were determined frequently.

In several control experiments, the effects of sodium barbital on the cardiac output and blood pressure were determined. In trained animals that had received no drugs except for the injection of procaine hydrochloride at the site of the introduction of a blood pressure cannula, the cardiac output and blood pressure were determined. Sodium barbital, 0.3 Gm. per kilogram of body weight, was then administered intravenously. The determinations were repeated thirty minutes later, ninety minutes later and at varying intervals thereafter. The administration of barbital was followed by an immediate increase in the pulse rate and a diminution in the pulse pressure. The cardiac output was usually greater thirty minutes after the giving of barbital than during the control period. Then it usually declined to a level slightly below that found in the control period and remained practically stationary for at least four or five hours. In experiments of this duration there was usually no further decline in blood pressure following the initial drop which occurred usually within ninety minutes after giving the barbital. The results in one of the experiments in which the effects of barbital alone was studied are given in table 1.

In the following experiments, an interval of at least ninety minutes separated the giving of the barbital and the initial determinations. It is believed that this excludes largely the alterations due to the barbital itself.

1. *The Effects of Hemorrhage.*⁴—After barbital was given and control determinations were made, whole blood which equaled 0.5 per cent of the body weight was removed from the femoral artery at one hour intervals. The early decrease in systolic pressure and rise in diastolic pressure which were found in the previous experiments¹ on

TABLE 1.—*The Effects of Barbital on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. Hg.	Mini-mum Blood Pressure, Mm. Hg.	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
3:20 p.m. (control)...	13.15	120	102.4	15.43	9.96	5.52	160	107	110.07	2.77%
3:57 p.m. (30 minutes after barbital).....	185	102.0	14.83	10.80	4.03	144	127	107.01	2.67%
4:57 p.m. (90 minutes after barbital).....	185	101.8	14.83	10.56	4.32	131	111	82.05	1.91%
7:45 p.m. (4 hr. 18 min. after barbital)	180	102.5	14.76	9.96	4.80	110	114	91.55	1.90%
9:30 p.m. (6 hr. after barbital).....	180	102.6	14.76	9.21	5.52	125	115	102.72	1.87%

TABLE 2.—*The Effects of Hemorrhage on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. Hg.	Mini-mum Blood Pressure, Mm. Hg.	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
11:30 a.m. (control)...	21.05	129	100.0	17.52	13.63	3.84	162	136	131.00	3.412
1:10 p.m. 0.5%.....	120	100.3	18.48	13.80	4.68	159	140	156.09	3.335
2:10 p.m. 1.0%.....	150	100.8	17.76	13.80	3.96	140	125	142.07	3.588
3:10 p.m. 1.5%.....	156	101.6	19.56	13.80	5.76	139	115	153.33	2.902
4:10 p.m. 2.0%.....	164	102.4	19.56	12.84	6.72	137	113	144.46	2.749
5:10 p.m. 2.5%.....	160	100.3	18.60	12.00	6.60	120	90	166.05	2.516
6:10 p.m. 3.0%.....	167	100.0	19.44	10.56	8.88	117	107	168.63	1.990
7:10 p.m. 3.5%.....	Died									

hemorrhage under morphine anesthesia were not present in these experiments, possibly because barbital itself causes a diminution in the pulse pressure. In the present experiments, definite reductions in the cardiac output preceded significant alterations in the blood pressure just as in the previous experiments in which morphine was used. Changes in pulse rate are probably unimportant since barbital alone usually causes an extremely fast rate. The results of one of the experiments in which the effects of hemorrhage were studied are given in table 2.

4. In one experiment the effects of the graded removal of blood plasma instead of whole blood were studied. The results were approximately the same in the two types of experiments.

2. *The Effects of Severe Trauma to an Extremity.*—The trauma was inflicted by striking the posterior extremities many times with a hammer. The skin was not torn and bones were not broken. The length of time during which the trauma was instituted was usually about fifteen minutes. The blood pressure usually rose slightly during the traumatization. The cardiac output always declined markedly before any definite reduction in the blood pressure occurred. The results of one of these experiments are given in table 3.

TABLE 3.—*The Effects of Trauma to an Extremity on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. of Hg	Mini-mum Blood Pressure, Mm. of Hg	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
10:45 a.m. (control)...	11.1	126	99.4	18.84	16.20	2.64	140	100	60.19	2,250
12:05 p.m. (control)...	142	99.4	21.36	18.36	3.00	145	120	64.34	2,145
12:45 to 1 p.m. trauma										
1:10 p.m. (10 minutes after trauma).....	118	98.6	22.56	17.88	4.68	154	124	62.96	1,345
1:40 p.m. (40 minutes after trauma).....	122	99.1	21.84	17.40	4.44	155	125	65.73	1,480
3:20 p.m. (140 minutes after trauma)...	124	100.2	22.20	12.48	9.72	125	105	68.03	700
5 p.m. (4 hours after trauma).....	21.36	5.04	16.32	86	75	80.49	493

TABLE 4.—*The Effects of Intestinal Trauma on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. of Hg	Mini-mum Blood Pressure, Mm. of Hg	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
12 noon (control)....	10.2	128	98.4	24.48	20.76	3.72	163	108	69.29	1,992
12:30 p.m. trauma begun at 1 p.m.	154	97.7	26.64	20.88	5.76	155	114	45.92	797
1:30 p.m.	162	98.0	27.00	15.00	12.00	130	110	34.44	257
2:15 p.m.	114	96.7	25.20	5.40	19.80	39	30	68.26	345

3. *The Effects of Trauma to the Intestines.*—The trauma was instituted by continuously mashing the intestines gently between the fingers after a midline abdominal incision had been made. In some of the experiments there was a definite decline in the blood pressure associated with the opening of the peritoneal cavity and the beginning of the trauma. In some of these experiments the blood pressure returned to or almost to the original level, while in others it remained definitely depressed. However, the alterations in the output of the heart were always much greater than the changes in the blood pressure. The results of an experiment in which there was a large decline in the cardiac

output before any definite alteration in the blood pressure occurred are given in table 4. The results of an experiment in which there was a drop in the blood pressure and a greater decline in the cardiac output are shown in table 5.

4. *The Effects of Burns.*—With the animals profoundly anesthetized by barbitol or by morphine and ether, burns were effected by the use of heated metal cauteries. During the time that the heat was being applied, the blood pressure usually fell slightly. This was not always the case, as in some instances it definitely rose. Studies were performed at vary-

TABLE 5.—*The Effects of Intestinal Trauma on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maximal Blood Pressure, Mm. Hg.	Minimal Blood Pressure, Mm. Hg.	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
10:30 a.m. (control)...	10.2	102	98.8	20.64	18.00	2.64	150	93	62.73	2,376
11:30 a.m. (control)...	102	98.6	10.02	16.92	8.00	162	106	66.42	2,214
11:45 a.m. (trauma begun at 12:15 p.m.)	108	98.1	20.76	15.72	5.04	110	83	70.10	1,570
12:45 p.m.	116	93.0	20.83	10.08	4.80	110	85	51.10	1,067
1:45 p.m.	128	98.2	23.88	15.06	7.92	124	92	55.35	699
2:45 p.m.	138	98.7	23.83	15.60	8.23	103	93	58.35	705
5:00 p.m.	130	97.5	22.08	6.48	15.60	98	68	41.51	266

TABLE 6.—*The Effects of Burns on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maximal Blood Pressure, Mm. Hg.	Minimal Blood Pressure, Mm. Hg.	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
11:00 a.m.	13.6	164	99.1	17.52	14.04	3.48	134	92	92.25	2,651
12:00 noon	130	100.8	21.06	12.09	9.87	126	98	112.54	1,140
1:30 p.m.	110	103.1	21.72	11.52	10.20	134	90	124.73	1,223
3:00 p.m.	103	100.9	22.20	7.20	15.00	114	72	116.23	774

ing intervals after the cessation of the burning. The cardiac output decreased markedly before there was a significant alteration in the blood pressure. The results of a typical experiment are given in table 6.

5. *The Effects of Histamine.*—After control determinations had been performed, histamine hydrochloride (Hoffmann-La Roche) was injected subcutaneously. The solution used consisted of 1 mg. of histamine per cubic centimeter of physiologic solution of sodium chloride. In most of the animals that were anesthetized by barbitol, 5 mg. produced a definite decline in the blood pressure. Larger amounts were usually required when morphine was the anesthetic. The alterations in the blood pressure following the injection of histamine were marked, while

the changes in the cardiac output were comparatively small. In some instances following the initial injection of histamine, the cardiac output was unaltered and the blood pressure definitely declined. The results of such an experiment are given in table 7. In other instances, there was an initial increase in the output of the heart despite the fact that there was a definite decline in the blood pressure. An example of this effect is given in table 8.

COMMENT

The present studies do not include determinations of the volume of blood. It appears to be well established and generally admitted that alterations in the volume of blood precede changes in blood pres-

TABLE 7.—*The Effects of Histamine on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. of Hg	Mini-mum Blood Pressure, Mm. of Hg	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
2 p.m. (control).....	16.52	140	98.4	20.64	17.04	3.60	147	120	96.86	2,691
3 p.m. (after 20 mg. of histamine).....	132	97.3	20.52	17.04	3.48	94	66	89.45	2,571
4 p.m. (after 25 mg. of histamine).....	164	95.7	21.12	16.80	4.32	73	56	92.62	2,144

TABLE 8.—*The Effects of Histamine on the Cardiac Output and Blood Pressure*

Time	Weight, Kg.	Pulse Rate per Min.	Temperature, F.	Arterial Oxygen, per Cent by Vol.	Venous Oxygen, per Cent by Vol.	Arterio-venous Difference, per Cent by Vol.	Maxi-mum Blood Pressure, Mm. of Hg	Mini-mum Blood Pressure, Mm. of Hg	Oxygen Consumption, Cc. per Min.	Cardiac Output, Cc. per Min.
3:40 p.m. (control)....	14.6	200	101.5	21.90	17.16	4.74	143	103	101.47	2,141
4:24 p.m. (after 5 mg. of histamine).....	180	102.0	21.24	16.80	4.44	100	61	123.33	2,895
5:07 p.m. (after 10 mg. of histamine).....	180	102.4	21.00	13.92	7.08	93	43	127.51	1,501

sure and cardiac output in the development of shock. The most generally used criterion as to the degree of shock is the systolic blood pressure. This is due in part to the fact that determinations of the blood volume and cardiac output are more difficult to perform, are less accurate and are more apt to result in harm to the patient. However, the fact that a large decrease in the output of the heart usually precedes a decline in pressure after the production of injury has not been recognized. Wiggers,⁵ in his studies on the initial stages of abdominal shock, stated: "As the contour of the intraventricular pressure curves

5. Wiggers, C. J.: Circulatory Failure: The Differentiation Between That Due to Shock and That Due to Other Causes, J. A. M. A. 70:503 (Feb. 23) 1918

do not alter, as the heart rate, if it undergoes any change, increases, and as the pulmonary arterial pressure remains unaltered, the conclusion is reached that the reduction in the blood content and fall of pressure in the arteries is not due to a decrease in the minute volume of the heart, but to a reduction in the total arterial resistance." That the output of the heart is lessened does not indicate that it is unable to perform its work, but rather that there is a smaller amount of blood returning to it because of the diminished volume of blood, and hence that it has a small output. Information concerning the cardiac output following injury stresses the serious nature of a declining blood pressure. When the systolic pressure reaches a level of 80 mm. of mercury the output of the heart is usually no more than one third of its original value.

Many observers who have studied shock produced by trauma to the intestines have commented on the decline in pressure that is frequently associated with the opening of the peritoneal cavity and the beginning of the trauma. In regard to the changes that are found Wiggers⁶ stated: "A glance at the results presented in this chart shows that while the preliminary stage of the experiment involving the abdominal incision and removal of the intestines produces temporary reactions and often leaves the arterial and venous pressures somewhat low, the changes are not sufficient to be considered as even an initial stage of circulatory failure." Similar alterations in the arterial pressure were found by us in some of the experiments on burns during the time that the injury was being instituted. It seems probable that the condition is closely related to that which is described as primary shock in which there is a temporary dilatation of many capillaries with a fall in blood pressure and most likely in cardiac output. For fear of misunderstanding we would like to emphasize at this point that this and the previous papers of this series are concerned with secondary shock and not with the low blood pressure that sometimes appears immediately on receipt of an injury.

The finding of most interest in these experiments is that after hemorrhage, after trauma to the intestines and to an extremity and after burns significant alterations in the cardiac output precede those in the blood pressure, whereas the reverse order is found when histamine is injected. It does not prove but is evidence that histamine is not responsible for the shock that develops after injury. The fact that the studies on hemorrhage and on trauma gave closely similar findings supports the results in previous experiments of this series in which the loss of fluid from the blood stream into the injured area was determined. It is realized that the present paper does not include studies on the products of protein decomposition which are slower in their action than histamine.

6. Wiggers, C. J.: The Initial and Progressive Stages of Circulatory Failure in Abdominal Shock, *Am. J. Physiol.* 45:485, 1918.

Such products may be responsible in part for the development of shock, and it is possible that they affect the cardiac output and blood pressure in the same manner as hemorrhage and trauma rather than like histamine. Neither do the present studies include determinations on the effects of very small amounts of histamine administered slowly. In regard to this point Professor Abel,⁷ in a recent personal communication, stated: "Professor Gibbs of Halifax who is spending some time in my laboratory tells me that when you inject into the blood stream of cats a weak solution of histamine you can inject a very large quantity slowly without causing any fall of blood pressure during an hour or an hour and a half. Indeed there may be a slight rise of blood pressure. . . . Then all at once the blood pressure falls quickly to a fatal level and the animal passes out." Since in some of our experiments with histamine there was an increase in cardiac output at a time when the blood pressure had definitely fallen, it seems unlikely that an increase in blood pressure would be accompanied by a decrease in the output of the heart. The experiments mentioned by Professor Abel were performed on cats, and it is known that dogs and cats do not exhibit identical reactions to histamine.

SUMMARY

The cardiac output and blood pressure have been determined repeatedly in experiments on the effects of (1) graded hemorrhages, (2) trauma to an extremity, (3) trauma to the intestines, (4) burns and (5) the subcutaneous injection of histamine. Hemorrhage and the various types of injury were associated with, first, a significant decline in the output of the heart, followed by a drop in the blood pressure. On the other hand, following the injection of histamine, the blood pressure declined first and the cardiac output subsequently. No evidence for the initiating action of histamine in the production of traumatic shock was found in these experiments.

PROTOCOLS

EXPERIMENT 1.—3:20 p. m., control determinations. 3:27 p. m., sodium barbital (3.9 Gm.) given. 3:57 p. m., thirty minutes after administration of barbital, determinations. 4:57 p. m., ninety minutes after barbital, determinations. 7:45 p. m., four hours and eighteen minutes after barbital, determinations. 9:30 p. m., six hours after barbital, determinations. Eleven hours later, the blood pressure had declined to 94 systolic and 80 diastolic.

EXPERIMENT 2.—8:00 a. m., sodium barbital (6.3 Gm.) given. 11:30 a. m., control determinations. 1:00 p. m., bled 105 cc. 1:10 p. m., determinations. 2:00 p. m., bled 105 cc. 2:10 p. m., determinations. This was repeated at hourly intervals, the dog dying at 7:10 p. m. after the removal of a total amount of blood equaling 3.5 per cent of the body weight.

7. Abel, John J.: Personal Communication to the author, 1930.

EXPERIMENT 3.—8:20 a. m., barbital (3.1 Gm.) given. 10:45 a. m., control determinations. 12:05 p. m., control determinations. 12:45 to 1 p. m., leg traumatized. 1:10 p. m., ten minutes after termination of trauma, determinations. 1:40, 3:20 and 5 p. m., determinations.

EXPERIMENT 4.—9 a. m., barbital (3 Gm.) given. 12 noon, control determinations. 12:30 p. m., peritoneal cavity opened and trauma begun. Trauma continued and determinations performed at 1, 1:30 and 2:15 p. m.

EXPERIMENT 5.—8:30 a. m., barbital (3 Gm.) given. 10:30 and 11:30 a. m., control determinations. 11:45 a. m., peritoneal cavity opened and trauma to the intestines begun. Trauma continued and determinations performed at 12:15, 12:45, 1:45, 2:45 and 5 p. m.

EXPERIMENT 6.—8:50 a. m., barbital (4.1 Gm.) given. 11 a. m., control determinations. 11:15 to 11:45 a. m., approximately one fourth of body surface burned. 12 noon and 1:30 p. m., determinations. 1:45 to 2 p. m., additional burning. 3 p. m., determinations.

EXPERIMENT 7.—10 a. m., barbital (4.9 Gm.) given. 2 p. m., control determinations. 2:40 p. m., 20 mg. of histamine given subcutaneously. 3 p. m., determinations. 3:10 p. m., 5 mg. of histamine. 4 p. m., determinations. The blood pressure remained depressed after the initial injection of histamine.

EXPERIMENT 8.—8:40 a. m., barbital (4.4 Gm.) given. 3:40 p. m., control determinations. 4:20 p. m., histamine (5 mg.) given subcutaneously. 4:24 p. m., determinations. 4:44 p. m., blood pressure still depressed; 5 mg. of histamine given subcutaneously. 5:07 p. m., determinations.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

E. STARR JUDD, M.D.
ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.
ROANOKE, VA.

JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES
AND

ALEXANDER B. HEPLER, M.D.
SEATTLE, WASH.

KIDNEY

Tumor.—Mackey¹ stated that hemangiomas of the kidney are rare but significant because of the urgent necessity at times of surgical procedures for severe hemorrhage. In a case of his a diagnosis of renal tumor was made because of symptoms of renal colic, severe unilateral hemorrhage and the shadow of a filling defect in the pyelogram. An angioma of the lower major calix was found.

Mackey reviewed from the literature 17 cases of renal angiomas which caused hemorrhage sufficiently severe to necessitate surgical treatment. The cases are classified according to their situations in order to determine whether they may be distinguished by any constant clinical feature. In 6 cases the wall of the renal pelvis was involved, and the suddenness and severity of the hemorrhage necessitated immediate intervention. In none of the 4 cases of angioma of the cortex or the pyramids did hemorrhage constitute a surgical emergency. There was no outstanding distinguishing feature, and the diagnosis rested on the exclusion of other causes of hematuria. It is justifiable to suspect angioma of the renal pelvis when unilateral hemorrhage occurs, especially if the patient is young, and without other urinary signs or symptoms dramatic in onset and so severe as to demand nephrectomy. Since subepithelial hemorrhage of the pelvis, a not uncommon cause of so-called essential hematuria, often responds to intrapelvic injection of silver nitrate, this treatment should be used.

1. Mackey, W. A.: Haemangioma of the Kidney, *Brit. J. Surg.* **18**:303 (Oct.) 1930.

Although angiomas are simple tumors and fairly small, the difficulty of localization or the inaccessibility of those involving the pelvis make conservative treatment by nephrotomy and cauterization unsatisfactory, and nephrectomy is usually indicated.

Bailey² stated that hemangioma of the kidney is difficult to localize and to treat conservatively, as illustrated by his case in which there was severe hemorrhage from the right kidney. Frequent attacks of hematuria made nephrectomy necessary. Three or four sections of the removed kidney were required before a small interpyramidal hemangioma was found in the upper pole.

[ED. NOTE.—Hemangiomas of the kidney are usually small, most of them being less than 1 cm. in diameter. They may cause profuse bleeding and are extremely difficult to recognize, since the pyelogram shows little that is abnormal. They are commonly on the border of the pelvis, so that they bleed into the pelvis. In most cases the tumor does not show any other pathologic change, except a small localized area of cavernous tissue.]

Schiffmann³ described a case of a combined sarcoma and hypernephroma of the kidney and of connective tissue of the pelvis. The patient, a woman, aged 68, was operated on and died three days later. The pelvic tumor lay retroperitoneally and measured 16 by 12 by 11 cm. Microscopically, it was found to consist of a capsule of connective tissue that sent septums into the depths of the tumor. One section consisted of a giant cell sarcoma, one of hypernephroma, and in one both types of tumor were closely associated. At necropsy a tumor of the left kidney with a thrombus in the renal vein was also found; this contained a necrosing fibroma, a large area of hypernephroma and a small island of giant cell sarcoma.

The pelvic tumor might have been a coincident primary growth or metastasis. The rests of suprarenal cortex are sometimes found in the pelvis, and such a tumor might be primary there, although it is more probable that the growth was metastatic. Schiffmann also stated as his belief that the tumor described is a true mixed tumor analogous to the carcinosarcoma of the uterus, and that the sarcoma cells are not derivatives of the hypernephroma.

Uluhogian⁴ reported a case of a rare tumor of the kidney called sarcoma carcinomatode by Billroth. A man, aged 43, experienced pain

2. Bailey, Hamilton: Haemangioma of the Kidney, *Brit. J. Urol.* **2**:375 (Dec.) 1930.

3. Schiffmann, J.: Hypernephroides Sarkom im Beckenbindegewebe-Hypernephroides Sarkom der Niere, *Arch. f. Gynäk.* **141**:685, 1930; abstr. in *Am. J. Cancer* **15**:492 (Jan.) 1931.

4. Uluhogian, L.: Sopra un caso di sarcoma alveolare o cosiddetto sarcoma carcinomatode del rene, *Tumori* **4**:230, 1930; abstr. in *Am. J. Cancer* **15**:493 (Jan.) 1931.

in the lumbar region, vomiting and hematuria. A large, firm, irregularly spherical tumor which moved with respiration was felt in the region of the left kidney, and nephrectomy was done. The kidney was three times the size of a normal kidney, and was covered with whitish nodules. On section, the tumor invaded the entire substance of the kidney. It was composed of polymorphic cells, some being similar to lymphocytes except that they had more protoplasm and a more irregular arrangement of chromatin, whereas others were large and clear, with oval nuclei and of various shapes. There were also some very large and irregularly shaped cells, which were arranged in compact masses or in loose alveolar formation, and contained none of the lipoid that characterized the cells of hypernephroma. In the larger nodules there was reticular stroma containing newly formed fibroblasts which separated the single tumor cells from each other.

Ulhogian stated his belief that this structure is characteristic of tumors of mesenchymal origin, and classified it as an alveolar sarcoma. Nine months after operation the patient died following local recurrence of pulmonary, hepatic and splenic metastasis.

Cysts.—Higgins⁵ stated that solitary cysts of the kidney are more common than the literature indicates. A roentgenogram may reveal the presence of a cyst, especially if it arises from the lower pole of the kidney. Preoperatively, a pyelogram may show a normal kidney, functional tests may be normal and there may be no urinary symptoms. Conservative renal surgical measures are the indicated treatment for this condition, either by dissection of the cyst away from the renal tissue, or by removal of the cyst together with a small wedge-shaped portion of the pole of the kidney. This will allow adequate approximation of the renal tissue. Nephrectomy should be performed, if deemed advisable, only in the presence of some coexisting renal pathologic condition, such as tumor, tuberculosis or calculi.

Stirling⁶ reviewed 31 cases of large, solitary hemorrhagic cysts of the kidney, including a case of his own. There were 17 men and 14 women in the series; the average age was 42 years. Twenty-two patients were cured, and 9 died. The right kidney was affected in 14 cases and the left in 17; the lower pole of the kidney was the site most frequently involved. The size of the cyst varied from that containing a few cubic centimeters of blood to that containing 4 liters (4,000 cc.).

Hemorrhagic renal cysts are extremely rare and should not be confused with solitary serous cysts. The wall of the cyst of the hemorrhagic type is thicker and the contents are different from those of the

5. Higgins, C. C.: Solitary Cysts of the Kidney, *Ann. Surg.* 93:868 (April) 1931.

6. Stirling, W. C.: Large Solitary Hemorrhagic Renal Cyst with Review of the Literature, *J. Urol.* 25:213 (Feb.) 1931.

serous type. Branch found solitary cysts in 4 per cent of cases in a series of necropsies, but Ewing pointed out that these included the common cysts of chronic nephritis. There are no pathognomonic symptoms of this condition. A dull, dragging pain with a sense of fullness, with the presence of an indefinite mass in the side, was present in practically all of the cases reported. Tenderness over the mass is also usually present.

Resection of the cyst with removal of a wedge-shaped area of renal tissue, including the mucous surface of the cyst, is the procedure of choice, provided the functioning capacity of the kidney is good. Owing to the enormous size of some of these cysts, rupture may take place in delivery. This may cause profuse hemorrhage which will require either packing or removal of the kidney. Aspiration of the contents of the cyst, if possible, helps in the prevention of soiling the operative field. As carcinoma was found in the wall of the cyst in some cases reported, the cyst should be examined immediately for any signs of malignancy.

Herbst and Vynalek⁷ stated that solitary serous renal cysts, although uncommon clinically, occur frequently enough to warrant consideration and elimination in all masses of the abdomen. A frequent roentgenographic observation is the outline of the shadow of the cyst itself, in close approximation to the solid renal shadow, and with density in marked contrast to that organ. A cyst large enough to cause clinical symptoms is often associated with an abnormal pyelogram, which, although seldom absolutely typical of the cyst, indicates pathologic changes in the kidneys. Resection of a wedge-shaped portion of renal tissue with the cyst is the treatment of choice. This method is less likely to be followed by secondary hemorrhage than an attempt at simple resection of the wall of the cyst. Nephrectomy should be done only in cases of extreme injury to the kidney, or if associated carcinoma is suspected.

Perinephritic Abscess.—Rolnick and Burstein⁸ reported 55 cases of perinephritic abscess. In a number of cases there was, from the first, definite evidence of tumor and bulging in the loin. In most of the cases a period of observation from a few days to ten weeks was required before diagnosis could be made and treatment instituted. The symptoms were fever, usually prolonged, fairly marked leukocytosis varying from 12,000 to 35,000 leukocytes, and, in most cases, costo-vertebral or abdominal tenderness which often appeared early. In 21 cases, previous renal disease or evidences of old renal involvement had

7. Herbst, Robert; and Vynalek, W. J.: Solitary Serous Renal Cysts, J. A. M.A. 96:597 (Feb. 21) 1931.

8. Rolnick, H. C., and Burstein, H. J.: Perinephritic Abscess: Review of a Series of Cases, J. Urol. 25:507 (May) 1931.

been noted. In 31 cases the lesions were apparently metastatic, although the foci of infection could not be determined in every case. In 4 of 5 cases in which the diagnosis of perinephritic abscess had been made, either pyonephrosis or calculous kidney was discovered later. Seven of the 55 patients died, 2 of these following nephrectomy as a secondary operation, thus the actual number of deaths due to perinephritic abscess was 5.

Several metastatic or hematogenous infections were readily diagnosed. Definite evidence was noted of bulging in the loin with a history of chills, fever and localized pain for three to eight weeks before the patients entered the hospital. Repeated urinalysis, cystoscopic examinations and pyelograms usually gave negative results during the early weeks of metastatic infection. Roentgenographic evidences of obscuring the lateral border of the psoas muscle by the abscess could not be demonstrated in four cases. In a number of cases delayed excursion, elevation and rigidity of the diaphragm on the side affected was noted, an observation of diagnostic value although the condition might be mistaken for a subphrenic abscess. Puncture and aspiration were the most valuable diagnostic aids. The diagnosis was determined in 8 of the 12 cases in which this was done.

In 6 cases in which pus from the abscess was examined, *Bacillus coli* was found in 2 cases, *Staphylococcus albus* in 2, *pneumococcus* in 1 and *Streptococcus hemolyticus* in 1. Cultures of the blood yielded positive results in 2 cases; in 1 case *Staphylococcus albus* and in the other *Streptococcus viridans* were found. The *staphylococcus* was the offending organism in most of the hematogenous infections. Nearly all the metastatic infections were secondary to furuncles, carbuncles or infections of superficial tissue.

Birdsall,⁹ in a review of various reports on perinephritic abscess, did not find a single instance in which primary infection developed independent of renal or extrarenal focus and resulted in the formation of a perinephritic abscess. Primary forms of perinephritic abscess may arise from trauma and injuries in the lumbar region when there is penetration or laceration. Secondary perinephritic suppuration may extend from extrarenal or renal foci or be carried by the blood or lymph channels. Braasch, in a review of 101 cases in which operation was performed for abscess in the perinephritic tissues, found that in 34 the condition was secondary to lesions outside the kidney. Habein reported 44 cases of perinephritic abscess, in 23 of which there was a history of boils, carbuncles, abscess and tonsillitis. In the remaining 21 cases a history of primary infection was not ascertained. Habein was of the opinion, however, that in 100 per cent of cases of perinephritic

9. Birdsall, J. C.: Perinephritic Abscess, *J. Urol.* 25:405 (April) 1931

abscess in which there is no evidence of primary renal disease, there is a history of such infection preceding the onset of abscess.

The characteristic symptoms of perinephritic abscess are pain, tenderness, tumor and fever. Chills, high fever and generalized aching pains may be present at the onset. The pain, steady, dull and aching, is at first confined to the loins; later, any movement of the trunk or leg on the affected side increases it.

Early diagnosis may avoid marked renal injury and general sepsis. Urinalysis and localizing symptoms lead to investigation of the affected kidney. Miller emphasized two points in the diagnosis; the existence of a fixed point of greatest tenderness over the renal triangle, and the exceptionally high leukocyte count. In 23 cases of his series the lowest count was 11,700 and the highest 48,800, with a general average of 24,700 in each cubic millimeter of blood. Roentgenograms disclosed that the spinal column curved away from the affected side; this occurs in other diseases of the kidney, and the outer margin of the psoas muscle is obscured by the abscess.

The mortality from perinephritic abscess depends on the cause, early diagnosis and promptness in evacuating the abscess. Hunt, in a series of 106 cases of perinephritic abscess observed at the Mayo Clinic, reported 7 (6.6 per cent) deaths in hospital. Twelve patients died from one month to five years after operation, a total mortality of 17.9 per cent up to five years after operation.

Early drainage is sufficient in most cases of perinephritic abscesses which develop from single cortical abscesses or are metastatic in origin.

[ED. NOTE.—Perinephritic abscesses are usually either acute, sub-acute or chronic. The chronic form is more common and, as a rule, more difficult to diagnose. The diagnosis of recent staphylococcus infection, such as furuncle, carbuncle, felon or sore throat, should be taken into consideration. In a large percentage of cases the etiology cannot be determined. The urine not uncommonly is normal and is not of aid in diagnosis. Exploratory puncture has been advocated by several surgeons recently. At times the pus is too thick to come through a needle, and a negative puncture does not rule out the presence of abscess. In some cases the abscess is small, near the upper pole of the kidney, and is located only with difficulty. Occasionally it is necessary to circle the kidney almost completely with the exploring finger before the abscess is found.]

Mycosis.—Lundquist¹⁰ reported a case of *Oidium* infection in which the symptoms of acute unilateral pyelonephritis were progressive

10. Lundquist, C. W.: On Primary Mycosis of the Kidney, *Brit. J. Urol.* 3:1 (March) 1931.

and severe enough to require nephrectomy. On section of the kidney numerous miliary abscesses were found. At the center of each was a fungous growth of a species of *Oidium*. Fungi or other bacteria were not found outside the abscesses.

Fungous infection of the kidney, especially primary, is extremely rare. Twelve cases of primary actinomycosis and 6 cases of nonactinomycotic fungoid disease have been reported, a case of sporotrichosis, 3 cases of infection due to *Oidium albicans*, 1 due to *Cryptococcus renalis* and a case of enantiothamnosis.

Cases have been too few to establish a clinical picture, although in primary renal actinomycosis prominent features are anemia, malaise and recurrent hematuria. There is absence of secondary vesical symptoms typical of tuberculosis, and there is marked perinephritis with infiltration and often fistulas. The diagnosis is rarely made preoperatively, although the fungi may be found in the urine. In nonactinomycotic infections, the clinical picture resembles that of acute suppurative pyelonephritis.

Pyelonephritis.—Mathé¹¹ stated that the distinguishing feature in the differential diagnosis is careful urinalysis. Too much reliance should not be placed on culture of the urine in ascertaining the nature of infection, as the colon bacillus will often overgrow and outshadow the staphylococcus, streptococcus and other organisms. Colon bacillus was recovered in 64 cases in which the stained smear had previously shown cocci alone or a mixed infection of cocci and bacilli.

Early catheterization and drainage in acute pyelitis is advisable in all cases in which acute hydronephrosis is suspected as being due chiefly to obstruction caused by congestion, which in turn results from inflammatory processes in the ureter and pelvis and lead to greater narrowing of the physiologically constructed portions of the ureter, notably its intramural portion and the ureteropelvic juncture.

The modern treatment of chronic pyelonephritis consists of eradication of all possible foci of infection, of the elimination of stasis in the upper and lower parts of the urinary tract, of drainage and lavage as a routine, alternating silver nitrate with the penetrating dyes, and the employment of local immunization by injection of the filtrate directly into the renal pelvis.

Of 347 cases observed for several years, the condition in 45 was not improved. In 30 cases there was stasis either in the upper or lower part of the urinary tract, which was a factor in lowering the resistance of the kidney, making it more susceptible to infection. In 115 cases improvement was only slight; relief from symptoms was more or less

11. Mathé, C. P.: *The Differential Diagnosis and Modern Treatment of Pyelonephritis*, J. Urol. 24:119 (Aug.) 1930.

transitory, but the urine remained infected. Because of progressive destruction of the kidney nephrectomy was performed in 15 cases; it was performed for pyonephrosis in 8 cases; for advanced pyelonephritis with recurrent stone formation in 3, and for persistent hemorrhagic pyelonephritis with atrophy and obliteration of the ureter in 2.

Hydronephrosis.—Schmidt¹² stated that the question of accessory renal vessels in relation to the production of hydronephrosis has been demonstrated during operations to be a fact. He observed that under pyeloscopy such a renal vessel filled with contrast fluid experienced difficulty in emptying, and that only a minimal amount of emptying ensued. In cases in which the vessels were sectioned and nephropexy performed, the patients usually obtained relief. A ureteropelvic anastomosis was done only in cases in which the accessory renal vessels were too large to section.

Beach¹³ produced paralysis of the ureter by application of nicotine to the free ureter of an anesthetized dog, and observed that dilatation of the segment followed if peristalsis persisted for at least a half hour. Segmental atony of the ureter in the rabbit and dog was produced experimentally, under aseptic technic, by removal of a segment of the ureter and reestablishment of its lumen by means of a glass cannula. Dilatation of the ureter both above and below the cannula and slight dilatation of the renal pelvis occurred in every case in which the cannula remained patent. Dilatation was noted as early as the third day after operation in the rabbit and after forty days in the dog, and persisted in the absence of infection and obstruction. Beach concluded that hydro-ureter and hydronephrosis were caused by experimentally produced atony of a segment of the ureter.

Calcified Arteries.—Fish and Hallock¹⁴ stated that calcification of the walls of the large intrarenal branches of the renal arteries in such a way as to give the roentgenologic appearance of calculi or tuberculous calcification is extremely rare. They reported a case that is of peculiar diagnostic interest to the roentgenologist, internist, surgeon and urologist, as shadows such as those shown in the roentgenogram are perhaps not infrequently seen, and, when associated with pyuria, hematuria or pain, offer a difficult diagnostic problem between calculous disease of the kidney and tuberculosis.

12. Schmidt, Albin: Die Rolle der akzessorischen Gefäße bei der Entstehung der Hydronephrose, *Ztschr. f. Urol.* **24**:414, 1930.

13. Beach, Watson: Atony of the Ureter in the Production of Hydronephrosis, *J. Urol.* **25**:367 (April) 1931.

14. Fish, G. W., and Hallock, L. A.: Calcification of Intrarenal Arteries Giving Roentgen Appearance of Calculi. *J. A. M. A.* **96**:1935 (June 6) 1931.

URETER

Calculi.—Tschernjak¹⁵ stated that conservative methods should always have preference over surgical procedures in cases of ureteral stone, because of the possibility of recurrence. In early days herbs, colon bacillus vaccines and various chemical reagents were suggested to dissolve the stones. Procedures such as enlarging the ureteral orifice, dilatation of the ureter by bougies, and the use of special instruments have been advocated at various times. Drinking large quantities of water so as to increase ureteral peristalsis has been advocated; Casper stated that with the ingestion of 1,500 cc. of water the ureter contracts 3,000 times in twenty-four hours. Increasing the water intake will raise the number of contractions to 10,000. Other observers believe that taking a large amount of water at one time will produce a sudden secretion of water. The introduction of substances such as glycerin into the ureter through a catheter appears to have been successful in some cases. The use of drugs hypodermically has been tried. Morphine has been found to increase instead of relax the ureteral muscular tonus. The use of paravertebral anesthesia has been mentioned, to produce temporary diuresis. Casper found this method of no avail; Tschernjak appeared to be partial to the use of drugs. Of 11 cases of ureteral calculus, there was successful passage of stone in 9 and partial success in 1. Pituitary extract definitely increases ureteral peristalsis and aids in expulsion of the stones. Stones in the renal pelvis are not affected by these conservative measures.

Barney and Chute¹⁶ studied a series of 123 cases in which the diagnosis was definitely stone in the ureter in the portion below the brim of the bony pelvis. There were 4 deaths (3.2 per cent) in the hospital, 2 of them during operation. Stones were removed from the ureter by cystoscopic manipulation in 35 of 68 cases.

Some of the requisites in the nonsurgical treatment of ureteral calculus are changing the position of the stone in the ureter so that the pressure of urine behind it will be more effective, dilating the ureteral lumen so that the stone may be forced through, or using an instrument which will grasp the stone and extract it. It is important to move the stone so that its long axis lies more or less parallel with the ureter. This may often be done by passing a ureteral catheter beyond the stone or up to it. Better results may be obtained by also dilating the ureter below the stone. The dilatation has been accomplished with one or two ureteral catheters of sizes as large as would

15. Tschernjak, I. S.: Zur Frage der konservativen Behandlung der Harnleitersteine. *Ztschr. f. Urol. Chir.* 31:20, 1930.

16. Barney, J. D., and Chute, Richard: The Management of Calculi in the Lower Ureter. *J. Urol.* 25:173 (Feb.) 1931.

pass, or with the largest Garceau catheter which would pass to or beyond the stone. In many instances the catheter was allowed to remain in place from twenty-four to seventy-two hours. These methods, combined with incisions of the orifice of the ureter, either with cystoscopic scissors or with diathermy electrode, were most frequently used.

Operation was performed seventy-three times on 72 patients with the removal of 80 stones. The incision just above and parallel to Poupart's ligament was used in 32 cases, and the mesial incision was used in 34 cases. The advantages of the mesial incision are that it permits operation, if necessary, on both ureters through one incision, and allows opening the ureter down to the ureterovesical juncture. With the incision above and parallel to Poupart's ligament it is not difficult to find the ureter, but it is impossible to open it at such a low point as in the mesial incision. The incisions require little, if any, hemostasis; they do not involve the peritoneal cavity and do not injure important structures. Hernia has never been observed to follow either operation.

Carson¹⁷ reported a case of large ureteral stone in which nephrectomy in two stages was performed. At the first operation 1,000 cc. of pus was removed by nephrostomy on the left side. At the second operation two calculi, one 4 cm. and one 8 cm., were removed from the left ureter. At the third operation the left kidney was removed, and four months later left ureterectomy was performed.

Tumor.—Davis and Sachs¹⁸ reported a case of primary epithelioma of the ureter, in which a positive diagnosis was made when the ureteral wall was still intact, before the tumor had become large, before any changes in the kidney secondary to obstruction had taken place and before visible implants in the lower part of the ureter or obstruction in the ureter to the passage of a catheter had occurred. The kidney was first removed, and the ureter was removed one year later. The tumor was a low grade, papillary squamous cell epithelioma, about 2.5 by 2 cm. in size. The bleeding was definitely established as being ureteral rather than renal. Clear urine was obtained from the renal pelvis coincident with the time that there was visible bleeding from the orifice of the ureter on the same side. This unique condition suggested the diagnosis of ureteral tumor.

Renner¹⁹ described a case of carcinosarcoma of the right ureter. The tumor rose approximately from the middle of the posterior wall of the ureter and filled practically the whole ureter as a sausage-shaped formation, about 2 cm. thick. It penetrated into the urinary bladder

17. Carson, W. J.: Giant Ureteral Calculi, *Ann. Surg.* **91**:141 (Jan.) 1930.

18. Davis, Edwin; and Sachs, Adolph: Primary Epithelioma of the Ureter, *J. A. M. A.* **96**:2096 (June 20) 1931.

19. Renner, M. J.: Primary Malignant Tumors of the Ureter, *Surg., Gynec. & Obst.* **52**:793 (April) 1931.

and ended in a round swelling about 6 cm. in diameter. The tumor of the ureter was considered to be a real carcinosarcoma, and it was assumed that local predisposition of the tissue was already present in early embryonic stage, thus causing formation of the growth.

Of other malignant growths, about 50 ureteral carcinomas and about 10 tumors of the mesenchyme, most of them malignant, have been reported up to the present.

Pyoureter.—Jeck²⁰ stated that pyoureter is caused chiefly by obstruction and injury to the nerve supply of the ureter resulting in absence of peristalsis and lack of tonus. The principal causative factor in most cases is ureteral stone. The relative occurrence of pyoureter, including even cases of stone, is small. It can be prevented by proper treatment of the ureter and its contents at the time of nephrectomy. A few cases may be successfully treated by conservative measures, such as fulguration and irrigation, but ureterectomy, especially complete ureterectomy, is indicated in most cases.

Plastic Operations.—Ormond²¹ presented the following as his personal conclusions regarding plastic operations on the ureter: in selected cases plastic operations on the ureteropelvic juncture are indicated, the type depending on the individual case. Nephropexy of some kind, as well as splinting of the ureter with catheters according to Peck's method, may be used in most cases. Pyelogram of the supposedly uninvolved kidney should be part of the diagnostic procedure in every case of hydronephrosis. In case of a markedly injured kidney or if patients are elderly, nephrectomy is preferable to plastic operation unless the other kidney is injured or is in an early stage of the same condition. If the patient cannot afford the expense of a long convalescence, the follow-up treatment, and the possible time loss and expense of a second operation, nephrectomy is to be preferred to a plastic operation in the presence of a normal function on the opposite side, even if patients are young. In cases of aberrant vessels, the procedure to be followed is to be decided by the size of the vessel; section in the case of small vessels, and transplantation of the ureter to the other side of the vessel in case of the larger vessels.

BLADDER

Tumors.—Higgins²² stated that the majority of benign tumors of the bladder reported in the literature have contained smooth muscle tissue. In a series of 38 cases, this element was present in 34; 4 were fibromas.

20. Jeck, H. S.: Pyo-Ureter, Surg., Gynec. & Obst. **52**:1158 (June) 1931.

21. Ormond, J. K.: Plastic Surgery of the Ureter, J. Urol. **25**:117 (Feb.) 1931.

22. Higgins, C. C.: Benign Tumors of the Bladder, Ann. Surg. **93**:896 (April) 1931.

Fibroma arises in the mucosa of the bladder; as it enlarges it grows out into the bladder. On microscopic examination the bundles of fibers are found to be closely packed, and a few blood vessels may be seen coursing in a direction parallel with the thick, fibrous bundles. These tumors may undergo calcification and necrosis on account of their lack of blood supply.

Leiomyomas are tumors composed chiefly of nonstriated or smooth muscle and resemble tumors of the uterus. In the cases reported, leiomyomas have varied from 1 to 5 cm. in diameter. They may be single or multiple. Grossly, these tumors consist of dense, firm nodules, which may or may not be pedunculated. The nodules are sharply demarcated from the wall of the bladder, their consistence depending on the ratio of muscle elements to the connective tissue. Microscopically, these tumors consist of smooth muscle fibers arranged in interlacing bundles. The stroma consists of connective tissue through which the blood vessels course.

Rhabdomyomas are tumors containing striated muscle, and histologically are more complex than other tumors of the bladder. These neoplasms are usually polypoid, single or multiple, and vary from 1 cm. in diameter to the size of a large polypus. Microscopically, they are edematous, with small, spindle-shaped cells, among which are scattered larger cells with striated protoplasm.

Angioma in the bladder resembles angioma found elsewhere in the body.

In most cases benign tumors arise in the region of the ureteral orifice or the trigone, although no portion of the bladder is exempt. In a few of the cases cited, the pedicle of the tumor was attached to the vertex of the bladder, and cases of benign tumor arising from the posterior and lateral walls of the bladder have been reported.

Benign tumors of the bladder usually do not present symptoms until they are of considerable size. Frequently they are not discovered except at necropsy. If the tumors have a long pedicle, or if they are near the vesical neck of the bladder, obstructive symptoms, indicating the presence of some pathologic condition of the bladder, may occur.

Benign tumor of the bladder can be determined by cystoscopic examination, although visualization is difficult in the case of an unusually large growth. Prior to operation the diagnosis of a malignant lesion is often made. If the tumor is large, the capacity of the bladder is markedly diminished. The cystoscopic appearance of a small tumor is quite different from that of a papilloma or malignant tumor. As a rule, bleeding is not marked, the bladder is less irritable and the tumor is smooth and glistening. There is usually no sloughing, and touching the tumor with a ureteral catheter does not cause as much bleeding as there would be if the tumor were malignant.

Excision of the tumor is the procedure of choice, a wide excision being made to assure complete removal in case unsuspected malignant transformation may be present.

[ED. NOTE.—Benign tumors of the bladder, as stated by Higgins, are comparatively rare. Angiomas and myomas are occasionally seen. The myomas are similar to myomas of the uterus. They are rarely pure, but generally are fibrous and benign. Profuse hematuria is a common symptom and occasionally is combined with a palpably obstructing tumor. Six of 41 cases reported by Concetti among children were myomas. These growths are generally on the trigone or posterior wall of the bladder and are often pedunculated. They are the most common of the connective tissue tumors of the bladder.]

Macalpine²³ reported 2 cases of hemangioma of the bladder. In 1 case the diagnosis was made, and treatment was carried out by cystoscopic examination without microscopic confirmation; in the other, partial resection of the bladder was done, and the diagnosis was confirmed by histologic examination.

The outstanding symptom is hematuria, which, when once established, tends to be continuous or to recur at intervals and becomes increasingly severe. In 4 of 20 cases reviewed death was due to exsanguination. This condition must be distinguished from vesical varices, which are simple vascular dilatations and hypertrophy without formation of new vessels. The bleeding is not profuse and does not tend to recur. Expectant treatment may be given.

The existence of nevoid tissue elsewhere aids in the diagnosis of vesical hemangioma. In Macalpine's second case, the colon, rectum, thigh, scrotum and penis were extensively involved.

Because the main bulk of the cavernous tissue occupies the muscularis and because cauterization opens deep vessels which cannot be sealed by electrode, transurethral electrocoagulation is reserved for small and superficial tumors. For the same reason, resection of the bladder, when feasible, is preferable to excision of the growth by cautery.

[ED. NOTE.—Hemangiomas of the bladder may be small and their only symptom a persistent profuse hematuria, or they may be extensive, penetrating into the perivesical tissue and simulating growths of other pelvic organs. In most cases they are composed of anastomosing dilated cysts filled with blood; in rare instances they occur as branching masses of apparently recently formed blood vessels, supported by fibromyxomatous stroma. Such tumors are comparatively rare. Watson

23. Macalpine, J. B.: Two Cases of Haemangioma of the Bladder. *Brit. J. Surg.* 18:205 (Oct.) 1930.

found only 2 in 653 cases reviewed; Albarran reviewed 3 cases from the literature and reported 1 of his own which occurred in a series of 106 cases of tumor of the bladder which he had observed. There were 3 cases of hemangiomas in a series of 262 cases of tumor of the bladder reported from the Mayo Clinic.]

Aschner²⁴ reported a case of carcinoma of the bladder in which an operation in two stages was done. At the first stage both ureters were transplanted into the sigmoid. Cystectomy was performed seventeen days later; the bladder, prostate gland, seminal vesicles and a massive carcinoma were removed en masse.

In commenting on Aschner's report, Barringer spoke of the high mortality in this type of operation (about 50 per cent) and suggested radium treatment which offers as much chance of cure, with a mortality of 3 or 4 per cent.

Aschner stated that under modern conditions the mortality would more correctly be 10 to 15 per cent.

Aschner²⁵ stated that cystoscopic biopsy furnishes reliable data as to the nature of tumors of the bladder in 97.5 per cent of cases. The unavoidable failures occur chiefly in cases of multiple tumors and papillomatosis. In the presence of a malignant lesion, prognosis cannot be made from biopsy material alone. A diagnosis of a malignant condition made at biopsy in a case simulating papilloma on cystoscopic examination and response to fulguration is an indication for treatment with radium or for surgical intervention. Classification based on cell grading alone is not practical for clinical purposes. The presence or absence of infiltration is apparently a more reliable guide to the gravity of the case.

The situation of a malignant tumor determines its resectability. If carcinoma is diagnosed on biopsy, and the condition warrants surgical intervention, segmental resection of the wall of the bladder is the procedure of choice. Failure to operate even when tumors are pedunculated has often resulted in recurrence. Stalk invasion and tumor cells in blood vessels at the base cannot be detected on gross examination.

Colston²⁶ stated that there is a general uniformity of opinion that all epithelial tumors of the bladder are potentially malignant. Bumpus stated that certain tumors that Broders classified as graded 1 and 2 in his carcinomas graded 1 to 4 can be successfully treated by electrocoagulation through the cystoscope. Bumpus does not use radium and

24. Aschner, P. W.: Carcinoma of the Bladder: Ureterosigmoidal Implantation, Total Cystectomy, *Am. J. Surg.* 8:1068 (May) 1930.

25. Aschner, P. W.: Clinical Applications of Bladder Tumor Pathology, *Surg., Gynec. & Obst.* 52:979 (May) 1931.

26. Colston, J. A. C.: The Treatment of Tumors of the Bladder, *Am. J. Roentgenol.* 25:375 (March) 1931.

treats the more malignant types of tumors by excision and diathermy. Hunt found that 65 per cent of the patients operated on for tumors of grade 1 and 2 are alive three years or more after operation, whereas only 34 per cent of those with tumors graded 3 and 4 were living after three years.

At the Brady Institute, tumors of the bladder are classified according to their appearance at cystoscopic examination. The presence of a definite pedicle is of significance when considering treatment and prognosis. Pedunculated tumors rarely infiltrate; there may occasionally be some direct extension of the growth from the pedicle and superficial infiltration may occur. This cystoscopic procedure has led to a classification of tumors as follows: pedunculated, which are usually not infiltrating but may rarely be so; sessile, which may be noninfiltrating or infiltrating, and true infiltrating tumors.

It is concluded that the presence or absence of infiltration is the most significant characteristic of any tumor of the bladder and must be determined as accurately as possible before treatment. Noninfiltrating tumors are best treated by a combination of endovesical electrotherapy and direct application of radium. By direct application of radium, resistant tumors may usually be made to respond promptly to the high frequency spark, which markedly diminishes the possibilities of recurrence. Infiltrating tumors should be treated by resection whenever this procedure can be done safely. When resection is impossible the tumor should be destroyed by diathermy through the open bladder, and radium seeds implanted throughout its base. Successful and intelligent treatment of tumors can be carried out only by knowledge of cystoscopic and electrotherapeutic methods, the technic of application, the results of radium and deep roentgen ray and thorough surgical experience in the treatment of such neoplasms.

Calculi.—Caulk²⁷ considered the advantages and disadvantages of the suprapubic removal of stone from the bladder as compared with litholapaxy or the crushing operation and evacuation of calculous fragments. The current opinion is that litholapaxy is indicated in all uncomplicated cases of stones in the bladder, without obstruction, without association of diverticulum, tumor of the bladder, intense cystitis or urethral stricture, and that surgical removal is the operation of choice in complicated cases.

The average age of patients with stone in the bladder was 56.6 years. The majority of stones occurred usually when the patients were between the ages of 40 and 70 years. One hundred ninety-seven of the patients (87.5 per cent) were men, and 28 (12.5 per cent) were women.

27. Caulk, J. R.: Litholapaxy: The Method of Preference for the Removal of Vesical Calculi, *Ann. Surg.* 93:891 (April) 1931.

There was associated enlargement of the prostate gland in 116 cases (51.4 per cent), including 20 cases of carcinoma of the prostate gland (17 per cent). Stricture of the urethra occurred in 17 cases (7.5 per cent), associated with prostatic hypertrophy in 7. Other conditions associated with stone were carcinoma of the bladder in 13 cases; diverticula of the bladder in 17; neurogenic bladder in 5; suprapubic fistula in 8; vesicovaginal fistula in 1 case; recto-urethral fistula in 1, and perineal fistula in 2 cases. Sixty-five per cent of the patients were classified as good risks, and 35 per cent as poor. Of the poor risks, 42 (60 per cent) were operated on by litholapaxy with 1 death (2.4 per cent), and 16 were treated suprapubically with 4 deaths (25 per cent). One hundred ninety-six operations were performed in the series of 225 cases. In 112 (57 per cent) of the 196 cases, litholapaxy was done; in 32, suprapubic cystotomy alone; in 52, cystotomy in conjunction with prostatectomy and other surgical procedures such as diverticulectomy, resections of the bladder for tumor, radium implantation or catheterization. Litholapaxy was performed in 44 cases in which prostatic hypertrophy was associated; 7 operations were done in cases with prostatic carcinoma, and 8 operations in cases with stricture of the urethra.

In 169 cases in the series the size and number of stones were noted. In 66 (39 per cent) the stones were multiple; cure followed litholapaxy in 60 per cent. In 14 cases (35 per cent) multiple stage operations were required. There were 82 stones either alone or multiple. The condition of 27 (33 per cent) of these patients was cured by litholapaxy.

In many of the simple cases a local urethral anesthetic is sufficient; there appears to be no necessity for a general anesthetic. In rare cases, spinal anesthesia is advisable. The chief structures to be protected during this operation are the urethra and the wall of the bladder. It is essential to crush as much as possible during one introduction of the lithotrite and then remove it for evacuation. It is seldom necessary to insert the lithotrite more than twice at one sitting. To protect the urethra from tears or injury resulting from fragments adhering to the instrument, the lithotrite is advanced into the bladder and when centered in the open bladder, the male and female blades are jammed together in order to throw off the impacted fragments and then are screwed together tightly before extraction.

Few complications resulted from litholapaxy in these cases; pyelonephritis occurred in 4.4 per cent, epididymitis in 4.4 per cent, hemorrhage in one case, periurethral abscess in 3 per cent and impacted calculus of urethra in 3 per cent. The average stay in the hospital in the 112 cases was ten days; in most of the uncomplicated cases, only two or three days.

Indications for the suprapubic operation are: large stones, stones which are adherent to the wall of the bladder and stones associated with other pathologic conditions, such as prostatic obstruction, stricture, diverticulum or tumor. The average stay in the hospital following suprapubic cystotomy was thirty-nine days. In 32 cases of simple cystotomy there was one death (3.1 per cent). In the 52 cases of cystotomy for stone in which prostatectomy or prostatectomy with resection of the bladder for tumor or for diverticulum was done, there were 7 deaths (13.4 per cent). In the 112 cases of litholapaxy there was 1 death.

Diverticulum.—Eisenstaedt and McDougall²⁸ stated that increased intracystic pressure due to obstruction or infection or both are significant in causation of hernia of the bladder through a congenitally weak area. Congenital diverticula do not present histologic characteristics to distinguish them from the acquired type. Complete surgical removal is indicated in all cases in which the general condition of the patient warrants operative intervention. Preliminary drainage offers little help in preparing a patient for radical resection of a diverticulum.

Exstrophy.—Walters²⁹ stated that 100 patients with exstrophy of the bladder have been operated on at the Mayo Clinic within the last thirty years. Seventy-three of these patients were operated on by a method described by C. H. Mayo. The procedure consists of transperitoneal transplantation of the ureters into the sigmoid, using a principle which Coffey described in transplantation of the common bile duct. The lower end of the ureter, for a distance of 2.5 to 3 cm. is carried in the wall of the sigmoid, between the muscular and mucosal layers of the intestine, so as to secure a valve-like action. In the experience at the clinic this operation has been attended by an extremely low mortality rate, and the evidences of ascending infection into the kidneys are practically negligible, even fifteen or twenty years after operation. Many of these operations were performed on adults, but the most propitious time is before the age of puberty. The patient should be at least 4 years of age and should have obtained sphincteric control of the feces. The safest procedure for children has been to transplant one ureter at a time. Preferably, the right ureter is transplanted at the first operation, and ten days or two weeks later, the left ureter is transplanted; in ten days the bladder can be removed. In the 73 cases in which both ureters have been transplanted, 3 patients (4.1 per cent) died in the hospital.

28. Eisenstaedt, J. S., and McDougall, T. G.: Bladder Diverticula with Especial Reference to Their Surgical Removal, *J. A. M. A.* **96**:831 (March 14) 1931.

29. Walters, Waltman: The Surgical Treatment of Some Congenital Abnormalities of the Genito-Urinary Tract. *Ann. Surg.* **93**:862 (April) 1931.

Paralysis.—Cathcart³⁰ reported a case of paralysis of the bladder due to spina bifida occulta. At cystoscopic examination residual urine, trabeculation of the bladder, relaxation of the internal sphincter and reduction of the expulsive force were noted. The condition was corrected surgically, with a good result.

Learmonth³¹ stated that in cord bladders in which spina bifida occulta is present, the osseous defect may be regarded as a primary factor in from 60 to 70 per cent of cases. The actual manifestation of the paralysis is due to mild but continued pressure on the roots of the sacral nerves, particularly the second, third and fourth sacral nerves, which provide motor and sensory fibers for the bladder. This pressure may be due to one of a number of causes. The most usual cause is the presence of a fibrocartilaginous band below the bony defect, which represents the persistent ligamentum flavum plus the rudimentary vertebral arch.

Tuberculosis.—Ferris³² stated that most authorities consider the bladder is never the primary focus of tuberculosis in the body. Vesical tuberculosis is usually secondary to involvement of the kidney, and less often to tuberculosis of the epididymis, prostate gland or seminal vesicles. He reported finding at necropsy tuberculosis of the bladder, unaccompanied by other demonstrable tuberculous involvement of the genito-urinary tract. Acute necrotic and exudative pulmonary tuberculosis and acute ulcerative tuberculous enteritis with multiple perforations causing general peritonitis were also present.

In the records of 2,062 necropsies at the New Haven Hospital, a tuberculous lesion of some type was mentioned in the anatomic diagnosis in 751 cases. In 568 cases the tuberculosis was healed or quiescent and was shown by an apical scar in the lung, or a calcified lymph node. In the remaining 183 cases, the lesions were active, and usually the primary cause of death. Ten cases of tuberculosis of the bladder were noted; in 7 cases one or both kidneys were involved, and in 6, infection of the prostate gland, seminal vesicles or epididymis was also present.

PROSTATE GLAND

Hypertrophy.—Cabot³³ rated the causes of death after prostatectomy as follows: (1) infection, including so-called pyelonephritis,

30. Cathcart, Edward: An Unusual Case of Paralysis of the Bladder, Proc. Staff Meet., Mayo Clinic 6:180 (March 25) 1931.

31. Learmonth, J. R.: Discussion, Proc. Staff Meet., Mayo Clinic 6:180 (March 25) 1931.

32. Ferris, H. W.: Tuberculosis of the Bladder: Report with Necropsy Findings of an Unusual Case Terminating in General Peritonitis from Perforated Tuberculous Ulcers of the Ileum, J. Urol. 25:497 (May) 1931.

33. Cabot, Hugh: Infection, the Central Problem in the Treatment of Prostatic Obstruction, Proc. Staff Meet., Mayo Clinic 6:163 (March 18) 1931.

together with the infections incident to operation, such as infection of the prevesical space, epididymitis and periurethritis; (2) various types of pneumonia and (3) various vascular accidents, including pulmonary embolism and cerebral hemorrhage.

It is Cabot's belief that too much attention is focused on avoidance of renal insufficiency in prostatectomy, and that infection has been allowed to assume significance in the cause of death. The more common types of infection contributing to mortality in prostatectomy are pyelonephritis, infection of the prevesical space, epididymitis and periurethritis, the last three of which can be partially or entirely abolished by attention to technic. Infection of the prevesical space can be avoided by approaching the bladder, after the skin, fascia and muscles have been separated, only in a transverse way, allowing the fascial protections of the prevesical space, where resistance to infection is low, to remain intact. Epididymitis is a serious complication, and is almost always due to extension of infection from the prostatic region to the epididymis along the vas deferens. It may be avoided by division of the vas deferens at the beginning of the institution of drainage, whether by urethral catheter or by suprapubic cystostomy. Periurethritis arises from irritation of the urethra, most commonly by an inlying catheter, but also by instrumentation incident to diagnosis. It is a handicap in the institution of urethral drainage, and perhaps cannot be entirely avoided if this method of drainage is to be used.

Infection of the urinary tract known as pyelonephritis should include infection of the bladder which always accompanies it. Pyelonephritis due to pure colon bacillus infection is seldom severe and rarely a cause of death. The admixture of various cocci together with *Proteus ammoniae* produce a more severe and highly fatal lesion.

In cases in which drainage by catheter is discontinued early or is never employed, and in which the drainage is done by the suprapubic route, infection of the urinary tract may not occur, or it is likely to be milder. In this group is the other common source of infection of the urinary tract, namely, that which follows removal of the prostate gland, an organ almost always infected by the time patients appear for operation. The removal of the prostate gland leaves a surface susceptible to infection on account of raw surfaces exposed to contamination. Infections appearing after prostatectomy are likely to be more severe, probably because the various cocci or the *Proteus* are more commonly the infecting organism.

Urethral drainage with the inlying catheter is associated with infection and jeopardizes somewhat the so-called one-stage prostatectomy as it is now carried out.

[ED. NOTE.—Cabot outlines succinctly the problem of infection in prostatic obstruction. Neff and Keyes showed that cystostomy in

two stages will avoid an enormous degree of prevesical space and infection of the abdominal wall. The ligation of the vasa as a preventive of epididymitis is now almost uniformly practiced. The use of the indwelling catheter undoubtedly predisposes to prostatitis and posterior urethritis of varying degree, as emphasized by Thomas and others. Hunt has shown that such infection probably has some value in vaccinating the patient against that infection which must take place in the prostate bed when the gland is removed, and hemostatic bags, packs and catheters are placed in contact with the raw surface of the prostatic capsule. It taxes the judgment of the surgeon to evaluate the factors for or against one or two-stage prostatectomy.]

Thomas, Exley and O'Brien³⁴ reported on a study of the preoperative and operative treatment, with observations at necropsy in 30 cases of hypertrophy of the prostate gland. Infection may be introduced into the urinary tract by any type of drainage of the bladder by catheter, and into the blood stream by traumatizing the urethra, both of which conditions contribute to the mortality in hypertrophy of the prostate gland. In 93 per cent of the records at necropsy, old or recent infection of the urinary tract was a significant factor in causing death. In none of the cases in this group was suprapubic drainage of the bladder alone carried out; in 93 per cent there was either periodic or permanent drainage of the urethra by catheter. Cardiovascular disease without infection of the urinary tract was a factor in producing death in only 7 per cent of the cases. Bronchopneumonia was the cause of death in 14 cases (46 per cent). In only 2 cases there was no evidence of a severe genito-urinary infection. Forty per cent of the total number of deaths occurred during preoperative treatment.

The authors concluded that the infection already present in the urinary tract, together with that which may be introduced by instrumentation, causes bacteremia which is responsible for the majority of deaths occurring during the treatment of hypertrophy of the prostate gland.

Seng³⁵ observed that in cases of prostatism in which the accepted normal of blood pressure deviated, the surgical risk was unfavorable, complications were likely to occur, and healing was prolonged. Five hundred and fourteen cases were studied. Estimations of blood pressure were divided into low, cases in which the systolic blood pressure was less than 140 mm. of mercury; normal, cases in which the systolic

34. Thomas, G. J.; Exley, E. W., and O'Brien, W. A.: Causes of Death Following Treatment for the Relief of Prostatic Obstruction, *J. Urol.* **25**:343 (March) 1931.

35. Seng, M. I.: Study of Blood Pressure in Prostatism Including Cardiovascular Changes, *J. Urol.* **25**:313 (March) 1931.

pressure was between 140 and 160, and high, cases in which the systolic pressure was 160 or more.

Of 454 cases in which prostatectomy was successfully performed, in which the condition was cured, the blood pressure was normal in 174 (38.1 per cent); it was low in 152 (33.4 per cent), and high in 128 (28.5 per cent). General examination of the cardiovascular system in these 454 cases disclosed arteriosclerosis in 22 per cent; enlargement of the left side of the heart in 18 per cent; myocarditis in 8 per cent; chronic endocarditis in 7 per cent, and enlargement of the right side of the heart in 1 per cent. In the cases in which blood pressure was low the average systolic pressure was low for prostatectomy. Renal function was good. After drainage the systolic pressure and pulse pressure dropped, but the renal function improved. In the normal group the average systolic and diastolic pressures were at the lower limits of normal. Pulse pressure indicated normal myocardium. Renal function was only slightly impaired. Following drainage, systolic, diastolic and pulse pressure dropped sharply, and renal function improved. After prostatectomy systolic and pulse pressures rose steadily, and renal function improved. In the group in which blood pressure was high the systolic and diastolic pressures and the pulse pressure were high. Renal function was good. Drainage lowered the systolic pressure markedly; diastolic and pulse pressures were less affected. Renal function improved. Patients with normal blood pressure have a resilient cardiovascular system. Following drainage, there is usually an initial fall in the pressure. With rest this should be partially recovered before prostatectomy. After removal of the prostate gland, a fall with recovery occurs.

There were 60 deaths in the series of 514 cases of hypertrophy of the prostate gland. Thirty-six deaths (60 per cent) occurred following prostatectomy; 18 (30 per cent) followed primary cystotomy only, and 6 (10 per cent) occurred in cases in which only drainage by indwelling catheter could be done. Thirty-six patients (7.34 per cent) died following prostatectomy. The mortality following only primary cystotomy or drainage by catheter was 45 per cent in the group in which blood pressure was low; 42.8 per cent in the group in which blood pressure was normal, and 31.5 per cent in the group in which the blood pressure was high. Operative mortality was 18 (6.74 per cent) in the group in which blood pressure was low, 20 (6.45 per cent) in the normal group, and 18 (9.21 per cent) in the group in which the pressure was high. The lowest operative mortality in relation to type of technic was 2 deaths (3.3 per cent) with suprapubic prostatectomy in one stage. Usually prostatectomy was performed by the two-stage suprapubic method; there were 32 deaths (7.58 per cent). The mor-

tality rate of perineal prostatectomy was 2 (25 per cent). In cases in which cystotomy only was done, 18 patients (51.4 per cent) died.

Necropsy revealed that 28 per cent of patients had had arteriosclerosis; 46 per cent, enlargement of the left side of the heart; 13 per cent, enlargement of the right side of the heart, and 20 per cent had had chronic endocarditis. Death in the group in which the blood pressure was low was apparently caused by cardiac deficiency rather than by increasing renal impairment. It occurred on an average of seventeen and five-tenths days after operation. Before drainage the systolic and pulse pressures were moderately low. Renal function was moderately impaired. After drainage there was practically no change in the pressure. Renal function as estimated by the condition of the blood was slightly more injured. Following prostatectomy, a marked drop in systolic and pulse pressures occurred, which was less marked in diastolic pressure. Renal function was impaired. In the case in which blood pressure was within normal range, the systolic pressure fell steadily after drainage; there was a further fall after prostatectomy. The diastolic pressure fell markedly after drainage with only moderate recovery after removal of the prostate gland. Death occurred from cardiac involvements and acute cardiac accidents rather than from renal failure, which is substantiated by the fact that death occurred on an average of ten and seven-tenths days after prostatectomy. If systolic pressure was high before operation, it rose after drainage, and fell abruptly after prostatectomy. There was a decided fall in diastolic pressure, with practically no recovery after removal of the prostate gland. Pulse pressure showed inversion of the usual curve, only more marked than in the other two groups. The renal function improved slightly following drainage without further recovery after prostatectomy. The mortality in this group was more definitely attributable to the combination of cardiovascular and renal deficiency. Death occurred on an average of seventeen and seven-tenths days following operation.

In the group in which the blood pressure was low, and in which prostatectomy was successful, complications were most common. The basis of 46 per cent of all complications was infection. Hemorrhage sufficiently severe to require packing of the prostatic cavity following prostatectomy occurred in 3 cases (0.6 per cent). Two were in the group in which blood pressure was low, and 1 in the group in which it was normal.

Seng concluded: The patient with normal blood pressure is the ideal surgical risk in prostatectomy. Deaths are principally due to cardiac and pulmonary involvements. If the patient has low blood pressure, prostatectomy is not so advisable. The wound heals sluggishly, and there is often advanced renal or cardiovascular breakdown, permitting only the simplest procedures to be undertaken. Cardiac and renal involve-

ments usually are the cause of death. Patients with high blood pressure are the least favorable surgical risks, as they are liable to cardiovascular, pulmonary and renal lesions.

Bacon, Kretschmer and Woodruff³⁶ stated that the electrocardiogram adds little information to indicate the preoperative risk in cases of obstruction of the prostate gland when severe cardiac disease is apparent on general examination. The hearts of elderly patients may be reported as normal on general examination, yet the electrocardiogram may show definite evidence of myocardial disease, a warning of the potential danger in attempting operation, particularly under general anesthesia.

Carcinoma.—Rovsing³⁷ stated that carcinoma of the prostate gland is one of the types that afford poorest operative results, owing, in most cases, to late diagnosis. Metastasis develops early, and for this the patient first seeks relief. If the carcinoma develops in the periurethral or accessory prostate gland, the symptoms are those of simple hypertrophy; if it lies hidden by the prostate gland proper, its real nature may escape the exploring finger. If the carcinoma develops in the prostate gland proper, it may grow for a long time without causing retention, but can easily be detected on rectal exploration.

Suprapubic prostatectomy is not recommended in cases of carcinoma of the prostate gland. In most cases enucleation is difficult because of firm adherence to the gland. The perineal route, which is usually chosen with the Young method, is no more radical than suprapubic enucleation. The advantages of the suprapubic route are as follows: diagnosis is possible regarding the extent of the tumor in the bladder by insertion of one finger into the bladder and another into the rectum; healing is more rapid than by the perineal route and fistulas are avoided, and if the tumor is inoperable, suprapubic drainage may be instituted. The relation of the tumor to the rectum is more easily determined by the perineal route, but hemostasis is more difficult and there is always danger of fistula. The nerves and vessels of the external sphincter are less exposed to injury by this route.

In 1928, Rovsing carried out the combined suprapubic and perineal operation. The bladder was resected in the median line down to the margin of the tumor and then cut through the wall of the bladder around the tumor and prostate gland and at a suitable distance from the tumor. Usually the wall of the bladder is not split to this extent, but in Rovsing's case the tumor extended too far into the bladder to permit implanting of the urethra at the usual site. The bladder was

36. Bacon, C. M.; Kretschmer, H. L., and Woodruff, Lewis: *Electrocardiographic Studies in Prostatic Obstruction*, J. Urol. 25:335 (March) 1931.

37. Rovsing, Christian: *Om behandlingen af cancer prostatae*, Ugesk. f. læger 92:578, 1930; abstr., Am. J. Cancer 15:498 (Jan.) 1931.

therefore closed anterior to the urethra, leaving a broad catheter in the latter.

The combined operation can be undertaken only if the patient's general condition permits such extensive intervention. Careful examination must be made for metastasis in the lungs and liver and in the glands of the pelvis, as manifested by neuralgic pains or edema of the lower limbs. The spinal column, especially its lumbar portion, and the bones of the pelvis must be examined, preferably by roentgen rays. If metastasis is present, radical operation does not offer cure and is not the proper procedure for relieving retention and other symptoms.

The primary operative mortality with the combined suprapubic-perineal operation is no greater than after simple prostatectomy. Rovsing's patient is well and working a year and a half after operation. In a number of cases fistulas and incontinence will occur.

Treatment by roentgen rays has given poor results in carcinoma of the prostate gland. As an adjunct to radium treatment and as a palliative measure in metastasis it is still used. Radium gives better palliative results than any other treatment, but cures are rare. Marion and Barringer have not had satisfactory results from radium treatment. Bumpus, Deming and Young are more optimistic about its use, principally as a palliative measure. For retention, catheterization rather than cystostomy is indicated in cases in which radium is to be applied later, and also in cases in which radium is not to be used.

The suprapubic fistula is indicated in cases in which urethral obstruction renders catheterization impossible, as well as in cases of total retention complicated with infection and in cases of severe hemorrhage from an ulcerated tumor. The suprapubic fistula may also afford relief in some cases of ulcerated tumor combined with cystitis in which the patient suffers intensely from tenesmus and pain on urination. Patients should be encouraged to get along without the fistula as long as possible, as inflammation of the bladder incident to this intervention hastens ulcer of the tumor. When this develops cystitis cannot be kept down, and the patient's suffering is increased.

Abscess.—Swan³⁸ stated that abscess of the prostate gland can manifest itself in a variety of ways. The entire gland does not always become abscessed; only a small part of one or more lobes may be involved. Symptoms may be almost entirely absent, local or generalized. The course of the disease is prolonged, although the acute stage may last a comparatively short time.

Swan believes that, except in cases in which surgical intervention is necessary due to acute retention, to the onset of high fever and

³⁸ Swan, C. S.: A Clinical Consideration of Prostatic Abscess, *J. Urol.* **25**: 413 (April) 1931.

chills, or to failure to relieve urgency and tenesmus of urination by palliative measures, nonoperative treatment should be the first method of choice. After the gland has been drained surgically, requiring hospitalization of about two weeks, there is always a period, usually prolonged, of necessary prostatic massage before the gland is free from infection. In most cases it is doubtful whether the operative drainage shortens the total duration of infection in the gland. Palliative treatment, consisting of hot rectal irrigations and frequent gentle massage, often eliminates the necessity of operative intervention in many cases. In some cases in which arthritis, chills or fever are not present before surgical intervention, all these conditions arise after operation, probably by a sudden throwing out of inflammatory products with their possible entry into the blood stream in the form of bacteremia.

(To be Concluded)

FRACTURES OF THE FEMUR

TREATMENT BY THE RUSSELL METHOD OF TRACTION:

REPORT OF TWENTY-ONE CASES *

HENRY J. LUND, M.D.

OAKLAND, CALIF.

My attention was first attracted to the Russell¹ method of treating fractures of the femur in 1927, on reading an article by Ryan² of Philadelphia. I herewith report the end-results in twenty-one cases in which this method of treatment was used at the Golden State Hospital, Los Angeles.

I have been impressed by the ease of application of this method and by the comfort it affords the patient. It facilitates the dressing of compound wounds and makes easy daily inspection and measurements. Early massage and other physical therapeutic measures may be given with excellent care of the soft structures and adjacent joints. The method may be used for practically all types of fractures of the femur. The end-results have been excellent, and a minimum of residual disabilities of the joint have occurred as compared with those following other methods.

The object of the Russell method depends on a natural and comfortable position of the limb with relatively small amount of extension to restore equilibrium of the muscle. Russell contended that when the muscles are extended to their normal length the fractured ends of the bones fall more or less into their natural alinement, provided there are no soft tissues interposed between the fragments.

In fractures of the femur, the shortening is due to tonic contraction of the long muscles of the thigh. These muscles have their origin on the pelvic girdle and traverse the entire thigh to be inserted into the tibia and fibula. The aims of traction, therefore, are to stretch these muscles to their normal length, to maintain correct alinement and to permit the bones to resume a more normal position. In order to do this, traction must be applied to the tibia and fibula where the muscles are inserted. Care must be taken that traction is not extended above the knee. Anxiety as regards the ligaments of the knee is needless, for the ligaments are attached to a fragment and cannot then be subjected to stretching. The entire extending force will fall on the muscles.

* Submitted for publication, Nov. 7, 1930.

1. Russell, R. H.: Fracture of the Femur: A Clinical Study, *Brit. J. Surg.* 11:491, 1924.

2. Ryan, T. J.: The Use of the Russell Apparatus in the Treatment of Fractures of the Shaft of the Femur, *Ann. Surg.* 85:529 (April) 1927.

In addition to this group of long muscles of the thigh, which are active in producing shortening, there are also the adductors, which are inserted into the linea aspera and adductor tubercle of the femur. The function of this group is to adduct and slightly rotate the thigh. The site of the fracture in regard to this group has much to do with alignment. If the line of fracture is high, the lower fragment is displaced medially; if low, the distal fragment is displaced laterally. In the mechanism of most fractures the shearing force is applied ventrally and from the lateral surface, so that naturally the fragments are forced backward and inward. The adductors tend to keep the displaced fragments in that position. This muscular action can be counteracted by varying the degree of adduction or abduction of the thigh, this being controlled by the position of a head to foot bar which is attached overhead to the Balkan frame.

THE APPARATUS AND TECHNIC OF APPLICATION

The material needed is a Balkan frame, four single pulleys 1 inch (2.5 cm.) in diameter, some window weight rope and 1, 2, 3 and 5 pound (0.5, 0.9, 1.4 and 2.3 Kg.) weights. Care should be taken that large pulleys and a small rope are used in order to minimize friction. The frame is attached to the bed, and 6 inch (15.24 cm.) blocks are placed under the foot of the bed. A head to foot bar is attached to the frame parallel to the fractured limb, which is abducted about 10 degrees. This bar carries pulley "A" at a point below the knee. A foot piece is attached to the frame which carries pulleys "B and D." A spreader and another pulley are needed, which are attached to the traction apparatus on the leg.

Some manipulation may be done, but anesthesia is not required. The leg is shaved and closely inspected for wounds. If these are present, they are thoroughly sterilized. Two strips of moleskin adhesive plaster are applied to the lateral and medial surfaces of the leg from the level of the tibial tuberosities distally to a spreader which is placed 2 inches (5 cm.) beyond the plantar surface of the foot. This spreader carries pulley "C." The spreader should be broad enough to prevent pressure on the malleoli by the adhesive traction straps. Thin cotton pads placed over the malleoli give added protection. A bandage is wrapped loosely over the adhesive and around the leg from the ankle to the knee.

The traction pulleys are placed in the following manner: Pulley "A" is suspended from the lower surface of the overhead bar at a point vertically above the junction of the tuberosities and shaft of the tibia. Pulleys "B" and "D" are attached separately to the traction bar beyond the foot of the bed. Pulley "C" is attached to the center of the distal surface of the spreader.

A broad canvas sling which has been padded with soft felt for comfort is passed beneath the knee. The canvas is firmly attached to a spreader or block. From this spreader the cord is passed as follows: through pulley "A"; through pulley "B" on the traction bar beyond the bed; through pulley "C" on the spreader; through pulley "D" on the traction bar beyond the foot of the bed where the weight is attached. The surgeon stands at the foot of the bed and tightens the ropes and applies the weights. A soft pillow is placed under the thigh and so adjusted as to prevent posterior angulation at the site of fracture. Another pillow is placed under the leg and achilles tendon so as to prevent the heel from touching the bed. The limb comes to rest in a position of not more than 10 degrees

of abduction and one-fourth normal flexion. In most of the cases reported here it was found that a straight pull gave better reduction than a pull through abduction. The position of the leg is, roughly, one parallel with the bed, the heel almost but not quite touching the bed.

Usually no difficulty is encountered with eversion, the upward traction on the knee, which is in a position of flexion, tending to prevent it. If too much eversion does occur, it can easily be corrected by attaching a small weight to the spreader at the foot.

Weights Required for Reduction and its Maintenance.—The weight first attached is 8 pounds (3.6 Kg.) for adults. Russell stated that for infants and young children he uses from $\frac{1}{2}$ to 4 pounds (0.25 to 1.8 Kg.) and for children up to 14 years of age 6 pounds (2.7 Kg.). At the end of three or four days roentgenograms are taken to check the progress of reduction. If the overriding persists, an extra 2 or 3 pounds are added. The weight required for maintaining

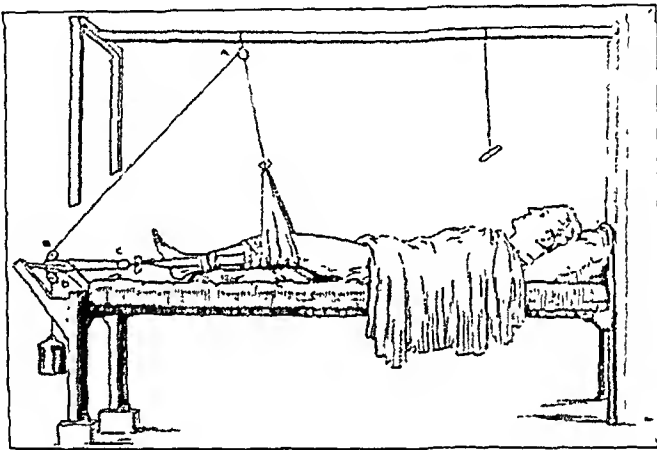


Fig. 1.—Russell traction apparatus. (From Brit. J. Surg. 11:492, 1924.)

correct reduction is determined by roentgenograms and frequent measurements. After the third week, 5 or 6 pounds of weight has been found to be sufficient to maintain reduction until clinical union has occurred. The mechanics of the traction method are such that the vertical and horizontal pull on the knee is practically twice the horizontal pull on the leg, a slight loss being due to friction of the rope and pulleys.

AFTER-CARE OF THE PATIENT

The apparatus is inspected daily, care being taken to see that the pillows are in place to prevent posterior bowing at the site of fracture and pressure of the heel on the bed.

When there is clinical evidence of firm union, traction is removed, and the patient is kept in bed for one week. During this time free motion is allowed, and he may sit on the edge of the bed with his legs hanging over. If union is not firm, pain is experienced at the site of the fracture, and angulation occurs. If roentgenograms demonstrate angulation, the traction is replaced.

If angulation has not taken place during the week after discontinuance of the traction, the patient is allowed to use crutches, usually without any accessory support. In certain cases in which the callus appears somewhat sparse and shows a lack of normal deposition of calcium, the patient has been fitted with a walking caliper splint which is worn until union is solid. Physical therapy is given in the form of electrical stimulation, both galvanism and faradism, together with diathermy. Massage and early motion at the joints are begun. As soon as the callus is sufficiently solid, weight-bearing on the limb is encouraged. First one crutch and then the other is replaced by a cane. Disability terminates when the patient can walk without the use of a cane and is able to resume the usual occupation with maximum function of the ankle, knee and hip joints.

Russell stated that whether the fracture is in the upper, middle or lower third of the femur, the treatment is exactly the same. The position of the limb and mode of extension is equally appropriate in all three conditions. The visible displacement, which is caused by muscular action, is only a transient phenomenon and will disappear as soon as the limb is placed in a comfortable position. He entirely disregards the proximal fragment and places the limb in a position that is natural and comfortable, with the assurance that the position natural and comfortable for the entire limb will be equally so for the proximal fragment in common with the rest, and that such position will be that which the proximal fragment will assume. The position is roughly one of about 4 inches (10.16 cm.) abduction at the hip with one-fourth normal flexion at the knee.

To recapitulate, in fractures of the femur, given a method of stretching out the muscles of the thigh to their normal length by an appliance that is perfectly comfortable, nothing will remain to be done except to overcome the force of gravity at the site of the fracture. The simplicity of this principle makes it the more practicable, and the method has proved to be so in practice.

ANALYSIS OF CASES

Twenty-one patients with fractures of the femur have been treated by the Russell method at the Golden State Hospital. The anatomic distribution of the fractures is shown in table 1.

In two of the cases, the fractures were compound. Thirteen cases showed certain degrees of comminution, four of which were severely comminuted. In four cases, the line of fracture extended into the lesser trochanter. The lesser trochanter was completely separated from its attachment in three cases. One of the patients had sustained a double fracture, the lines of fracture being through the proximal and distal thirds, respectively. In case 3, both femurs were fractured.

Most of the patients suffered from varying degrees of shock, three to a marked degree. Other injuries were sustained in the majority of the cases, the nature of which are given in table 2.

The after-care of the patients presented certain medical complications as shown in table 3.

TABLE 1.—*Anatomic Distribution of Fractures*

Location	Number
Intertrochanteric.....	3
Peritrochanteric.....	2
Shaft { Proximal one-third.....	7
{ Middle one-third.....	7
{ Distal one-third.....	4
Total.....	23

TABLE 2.—*Other Injuries Sustained By Patients*

Injury	Number
Severe contusions of the thigh.....	4
Lacerations of the scalp.....	3
Cerebral concussion.....	3
Fracture of the humerus.....	2
Fracture of the ribs.....	2
Fracture of the radius-ulna.....	2
Rupture of the spleen.....	1
Compound fracture of the tibia-fibula.....	1
Acute sprain of the knee.....	1
Fracture of the radial styloid.....	1
Lacerations of the forearm.....	1
Paralysis of the peroneal nerve.....	1

TABLE 3.—*Complications Presented*

Complication	Number
Hypertrophic arthritis.....	5
Arteriosclerosis with hypertension.....	3
Acute bronchitis.....	2
Cystitis.....	2
Myocarditis with decompensation.....	1
Acute retention with prostatic hypertrophy.....	1
Syphilis.....	1

In none of these cases did decubital ulcers develop. The patient in case 8 was about ready to resume work when he slipped and fell down a flight of stairs, refracturing the femur. The line of fracture was through the recently hardened callus. Four of these patients had been treated at other hospitals prior to their examination at the Golden State Hospital.

1. The patient in case 3 sustained a fracture of the shafts of both femora on Aug. 3, 1927. He was treated by manual reduction and the

application of a plaster body cast. He was transferred to the Golden State Hospital thirteen days after the injury, at which time measurements showed 2 inches of shortening.

2. The patient in case 7 sustained a fracture of the shaft of the right femur on July 11, 1927. He was treated by traction on a modified Thomas splint. He was transferred to the Golden State Hospital fifty-one days after the injury, at which time measurements showed 1 inch of shortening.

3. The patient in case 16 sustained a fracture of his left femur in the subtrochanteric region on March 12, 1929. Traction was unsuccessful, so an open reduction was performed on March 31, and the fragments held in position by a Lane plate. The cast was removed at the end of four weeks, and the patient was allowed to use crutches. He was transferred to the Golden State Hospital on May 14, two months after the injury. Examination showed considerable angulation and 1 inch of shortening.

4. The patient in case 18 sustained a fracture of the right femur in the intertrochanteric region on Dec. 5, 1929. The fracture was immobilized by a plaster body cast. He was transferred to the Golden State Hospital after ten days, when measurements showed 1 inch of shortening.

With the exception of these four cases, the traction was applied the same day that the accident occurred.

Nineteen of the patients treated were males; two were females. The average age was 42, the youngest patient being 17 and the oldest 74.

One patient, a woman, aged 74, died. She was in a state of profound shock and failed to respond to treatment.

All the patients were treated at the Golden State Hospital, Los Angeles, under the direction of Dr. Sam Herzikoff, chief surgeon, except the patient in case 21 who was one of Dr. Herzikoff's private patients and was treated at home, the Balkan frame and other apparatus having been supplied from the hospital.

The patient in case 22 is still under treatment. The case is introduced to show the rapidity and ease with which impaction may be reduced and an almost perfect alinement obtained through the use of 8 pounds of weight, according to the Russell method.

The accompanying illustrations are sepia-wash drawings of actual roentgenogram tracings, and were made by me.

A résumé of the histories of the cases follows:

CASE 1.—J. M., a youth, aged 17, was injured on April 18, 1929, when the motorcycle on which he was riding collided with an automobile. He was unconscious for forty-five minutes. Examination showed the following injuries: (1)

fracture of the left femur, (2) severe laceration of the scalp with cerebral concussion, (3) contusions of the upper part of the abdomen and (4) generalized contusions of the body and abrasions of the skin.

The patient was in marked state of shock. Roentgenograms of the left femur showed an oblique spiral fracture at the junction of the middle and upper thirds with overriding of about $1\frac{1}{2}$ inches (3.77 cm.). The upper fragment was displaced anteriorly and inward. Russell traction was applied with 8 pounds of weight. On April 20, the patient complained of severe pain in the left upper quadrant of the abdomen and in the left shoulder. An exploratory laparotomy

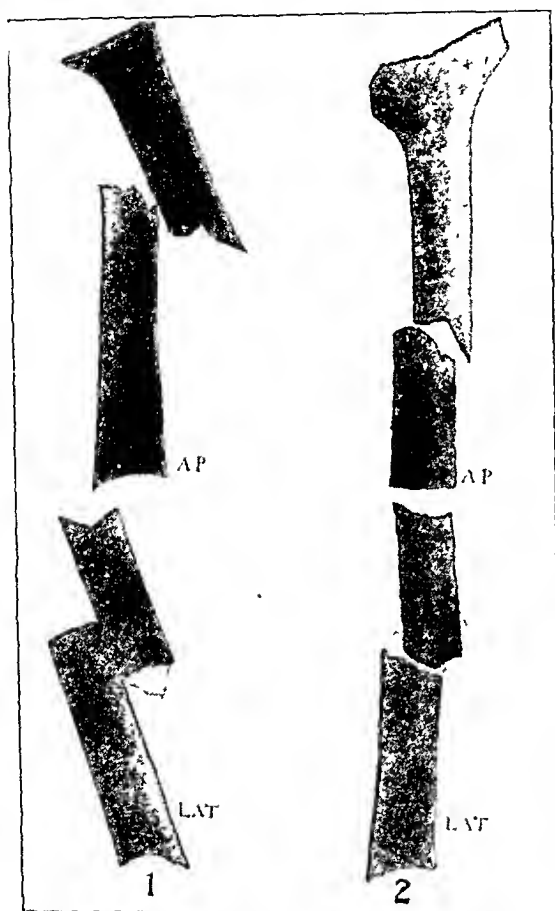


Fig. 2 (case 1).—Roentgenograms taken on: 1, April 18, 1929; 2, June 24, 1929.

was done, and a ruptured spleen removed. Recovery was uneventful. Following this operation, the patient's left leg was replaced in Russell traction. Roentgenograms taken on June 24, nine and one-half weeks after injury, showed abundant callus, particularly along the external surface. Alinement was good with slight angulation at the site of the fracture. There was slight inward and backward displacement of the distal fragment, but no shortening. Clinical examination showed firm union. Traction was removed. Motion in the ankle joint was normal, and motion in the knee joint showed complete extension with flexion of about 75 degrees. Measurements showed the left limb to be $\frac{1}{4}$ inch (0.63 cm.) shorter than the right. The patient was given intensive physical therapy and allowed to use crutches. No protective brace was applied. The patient returned

to work on Jan. 23, 1930, nine months after injury. Examination showed that he walked without a limp. The limbs were normal externally except for slight atrophy of the muscle of the left thigh. The motion of the hip, ankle and knee joints was within normal range.

CASE 2.—J. P., a man, aged 54, was injured on April 4, 1929, when a heavy steel girder fell from a dolly on which it was being carried and struck the patient's right thigh. Examination revealed: (1) fracture of the right femur and (2) fracture of the right radial styloid. The roentgenograms showed an

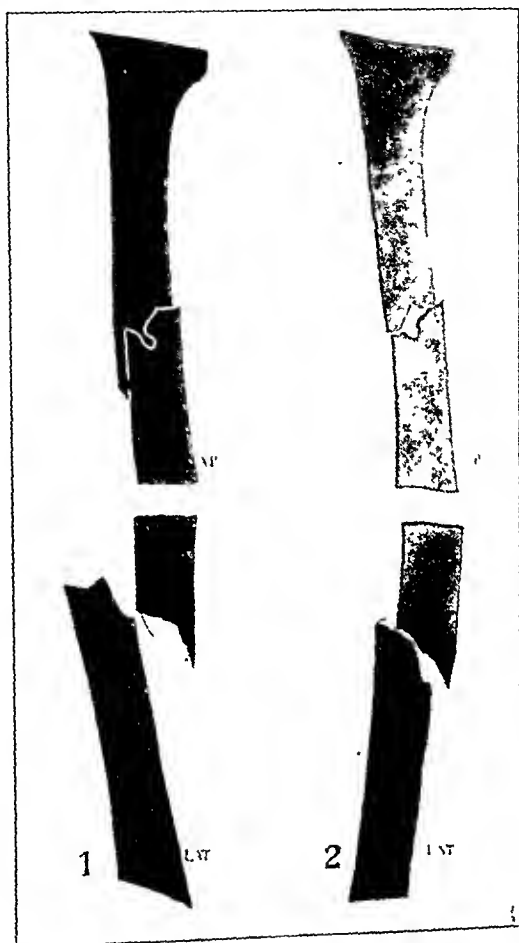


Fig. 3 (case 2).—Roentgenograms taken on: 1, April 4, 1929; 2, June 4, 1929.

oblique fracture of the midportion of the femoral shaft with overriding of about $1\frac{1}{2}$ inches. The distal fragment was displaced posteriorly and slightly inward. Russell traction was applied with 8 pounds of weight. Roentgenograms taken on April 11 showed that the overriding had not been completely corrected, so 3 additional pounds of weight was added. Roentgenograms taken on May 11 showed good alinement with end to end apposition. The additional weight was removed. Examination on June 4, nine weeks after injury, showed firm clinical union. Traction was removed. The roentgenograms showed the presence of abundant callus. The alinement was good, and the overriding was corrected. The motion of the ankle was normal, while motion of the knee showed normal extension with flexion of about 25 per cent. A walking caliper splint was applied.

and the patient was allowed to use crutches. He was given intensive physical therapy. During convalescence, he complained of moderate swelling of the entire extremity. The crutches were gradually discarded. Early in September, 1929, five months after the accident, the patient began to remove the brace and to bear weight on the injured member. He returned to light work on Nov. 14, 1929, seven and one-half months following the accident. Examination showed a slight weakness of the right lower extremity. The patient walked without a limp, and measurements showed the length of the lower extremities to be equal. Motion of the ankle and hip was normal. Flexion of the right knee was impaired 10 per cent.

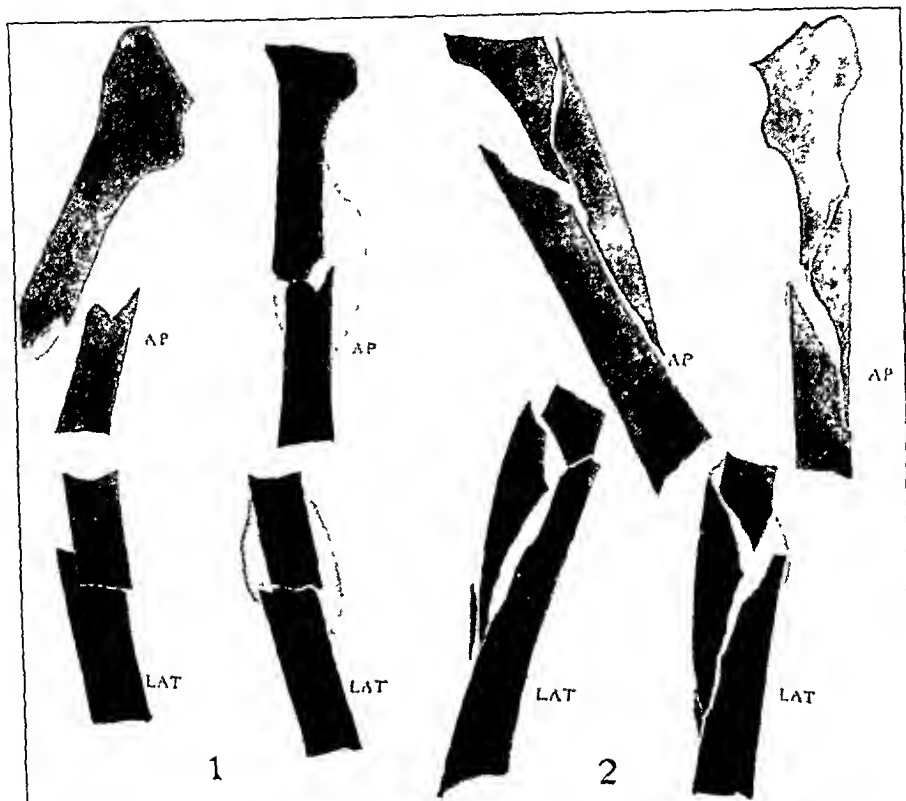


Fig. 4 (case 3).—Roentgenograms of the left femur taken on: 1, Aug. 3 and Sept. 28, 1927; 2, roentgenograms of the right femur.

CASE 3.—J. B., a youth, aged 19, was injured on Aug. 3, 1927, when an automobile in which he was riding skidded from the highway over an embankment. The patient was rendered unconscious. He was taken to a nearby hospital, where he was placed in a body cast; on August 16, he was transferred to the Golden State Hospital. Examination showed the following injuries: (1) fractures of the shafts of both femora, (2) fracture of the neck of the right humerus and (3) fracture of the right first and left second ribs. The left femur showed a long comminuted spiral fracture involving about 9 inches (22.9 cm.) of the shaft, the distal fragment being displaced inward and posteriorly the width of the shaft. A large triangular fragment 8 inches (20.3 cm.) long was detached from the upper and external portion of the femur, the upper level of this fragment being opposite

the base of the lesser trochanter, while the lower level was at the junction of the middle and lower thirds of the shaft. The fragments were overriding about 2 inches and were badly malaligned.

The right femur showed an irregular transverse fracture of the shaft through the junction of the upper and middle thirds. The ends were wholly displaced, and the fragments were overriding about 2 inches. The distal fragment was displaced inward and posteriorly.

Russell traction was applied with 8 pounds of weight to each extremity. Examination on September 28, eight weeks after injury, showed firm clinical

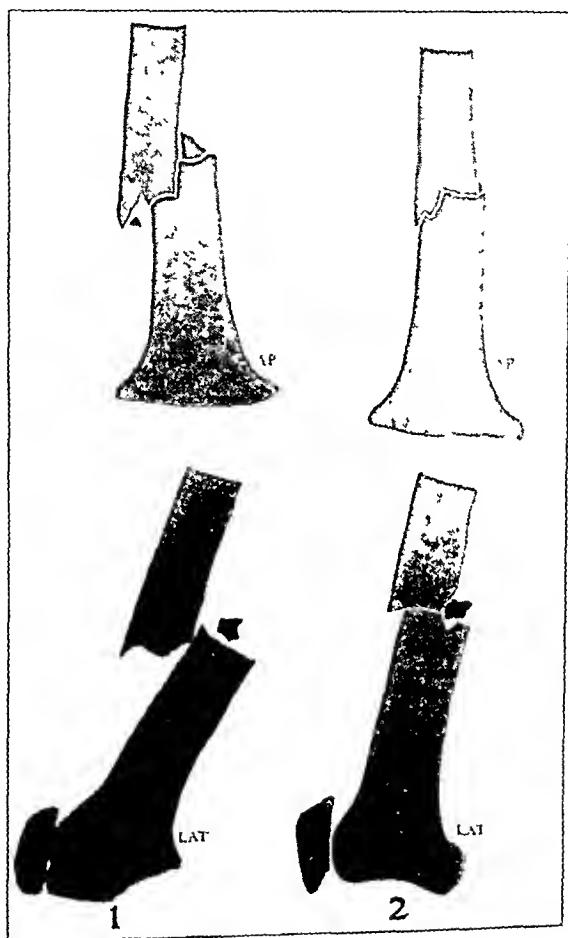


Fig. 5 (case 4).—Roentgenograms taken on: 1, June 21, 1929; 2, Sept. 9, 1929.

union. The roentgenograms showed good alinement with correction of the overriding. There was a marked formation of callus. Clinically, the legs were straight, and measurements showed them to be of practically the same length. Motion of both ankles was normal, while motion of both knees showed complete extension with flexion of about 60 per cent. The patient was able to raise both legs from the bed. He was allowed to use crutches. He was discharged from the hospital on October 14. On October 21, he discarded his crutches for a cane, and on November 22, he walked without support, complaining only of tiring easily. He returned to work on Feb. 1, 1928, six months after the accident. The muscle tone was good. He walked without a limp. The measurements showed

the legs to be of the same length, though the patient claimed he was 1 inch shorter than before the accident. No pain or tenderness was felt at the site of the fractures. Motion of the ankle, knee and hip was normal.

CASE 4.—F. G., a youth, aged 18, was injured on June 21, 1929, when he cranked his truck while it was in gear. The truck lurched ahead, crushing his right thigh against a building. The roentgenograms showed a transverse fracture of the right femur at the junction of the middle and lower thirds. There was backward and inward displacement of the distal fragment with complete separation of the fragments. There was overriding of 1 inch. A free fragment was seen lying on the upper surface of the lower fragment. Russell traction was applied lying on the upper surface of the lower fragment. Russell traction was applied with 8 pounds of weight. Roentgenograms taken on June 25 showed that the overriding was not completely corrected. Three additional pounds of weight was added. On September 9, eleven weeks after injury, examination showed firm clinical union. Traction was removed. The roentgenograms showed consider-

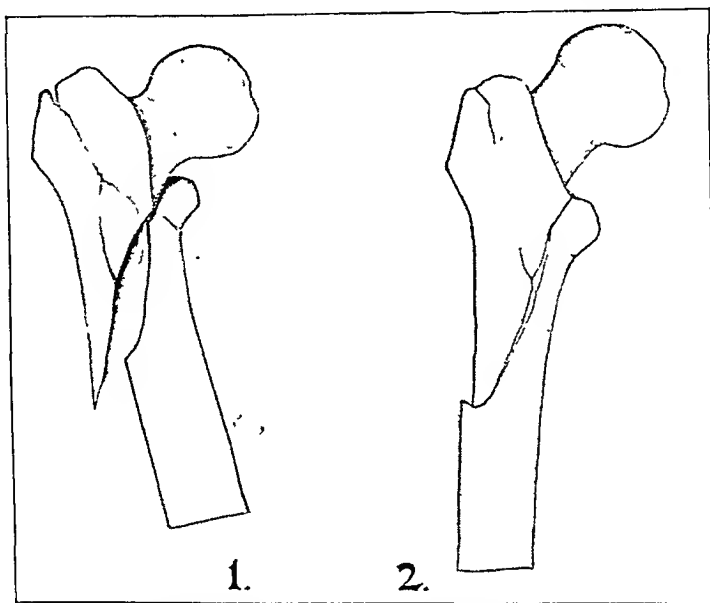


Fig. 6 (case 5).—Roentgenograms taken on: 1, May 17, 1927; 2, Aug. 24, 1927.

able callus. There was slight backward displacement of the distal fragment about one-third the width of the shaft and slight internal displacement of the upper fragment. Apposition was good. The patient was allowed to remain in bed for ten days, when roentgenograms showed no increase in deformity. He was then allowed to use crutches. No protective brace was applied. Motion of the ankle was normal, while that of the knee showed complete extension with flexion of about 35 per cent. The patient was referred to the physical therapy department. He was discharged from the hospital on September 30. On December 1, he began to bear weight, and on Feb. 21, 1930, eight months after the injury, he returned to light work. His only complaint was slight weakness of the right lower extremity with soreness at the site of the fracture at the end of the day. Examination on March 21 showed that the patient walked without a limp. There was no muscular atrophy. Measurements of the limbs showed the right one to be about $\frac{1}{2}$ inch shorter than the left. The motion of the ankle, knee and hip was normal.

CASE 5.—J. D., a man, aged 31, was injured on May 17, 1927, when a plank on which he was walking broke, and he fell 18 feet to the ground. The plank followed him and struck his right thigh. Examination showed: (1) fracture of the right femur and (2) clinical signs of syphilis (saddle nose, perforated septum, penile scars). The Wassermann reaction of the blood was 3 plus. The roentgenograms showed a long oblique fracture of the upper one third of the shaft of the right femur extending to the level of the lesser trochanter. The distal fragment was displaced inward and upward so that the fragments were overriding about 1 inch. There was a secondary line of fracture through the greater trochanter and another at



Fig. 7 (case 6).—Roentgenograms taken on: 1, Nov. 26, 1928; 2, Jan. 22, 1929.

the base of the lesser trochanter. Russell traction was applied with 8 pounds of weight, and antisyphilitic treatment was instituted. On July 6, seven weeks after the injury, roentgenograms showed excellent position and alinement with apparent union, so that traction was removed. The fragments, however, did not remain in position so that traction had to be reapplied. On August 24, fourteen weeks after injury, traction was removed. The roentgenograms showed excellent alinement and position. Examination showed firm clinical union. The patient was fitted with a walking caliper splint and allowed to use crutches. On November 7, the caliper splint was removed, and the patient used only a cane. He complained of pain in the right groin. On Feb. 4, 1928, nine months after fracture, he returned to work. He walked without a limp. There was slight atrophy of the muscle of

the right thigh. The measurements showed the right limb to be $\frac{1}{4}$ inch shorter than the left. Motion of the hip, ankle and knee was normal.

CASE 6.—R. D., a youth, aged 19, was injured on Nov. 26, 1928, when a 20 pound block of ice fell from the top of a refrigerating car and struck his right thigh. The roentgenograms showed a comminuted fracture of the shaft of the right femur at about its middle third. There was complete separation of the ends of the fracture with overriding of about 2 inches. There was marked inward angulation with the proximal fragment pushed inward and overriding the distal fragment anteriorly. The upper 2 inches of the lower fragment was badly com-

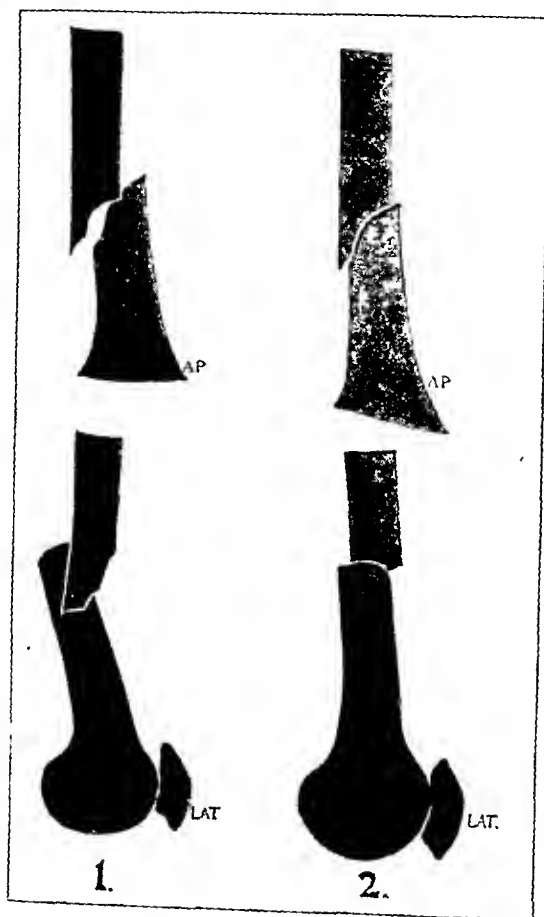


Fig. 8 (case 7).—Roentgenograms taken on: 1, July 11, 1927; 2, Oct. 19, 1927.

minuted. Russell traction was applied with 8 pounds of weight. Roentgenograms on December 15 showed that the overriding had been practically corrected. There was still, however, considerable inward angulation, so that 3 pounds of side traction was placed at the site of the fracture. Roentgenograms taken on Jan. 22, 1929, eight weeks after fracture, showed considerable callus. Alinement was satisfactory, though slight inward and backward angulation still persisted. Clinically firm union was present, so traction was removed, and the patient was allowed to use crutches. No supporting splint was applied. Motion of the ankle was normal. The knee could be flexed to the right angle. On February 21, a cane was substituted for crutches; on March 3, the cane was discarded. The patient returned to work on May 13, five and one-half months after fracture. Examina-

tion showed slight fullness at the site of the fracture due to bone prominence immediately beneath the soft tissues in front of the middle one third of the thigh. The patient walked with a very slight limp. Measurements showed the right thigh to be shorter than the left by $\frac{1}{2}$ inch. Motion in the hip, knee and ankle was normal.

CASE 7.—J. N., a man, aged 25, was injured on July 11, 1927, when a heavy water tank which he was helping to unload slipped from the wagon and fell across his right thigh. He was taken to a nearby hospital where the limb was placed in a modified Thomas splint; on August 31, he was transferred to the Golden State Hospital. Roentgenograms taken on September 2, showed an oblique fracture of the shaft of the right femur about $5\frac{1}{2}$ inches (14 cm.) above the knee joint. The distal fragment was displaced the width of the proximal fragment and angulated posteriorly, overriding the proximal fragment about 1 inch. There was no sign of callus. Russell traction was applied with 8 pounds of weight. Roentgenograms taken on September 13 showed greatly improved alinement but considerable external bowing. Three pounds of lateral pull was attached. On October 19, thirteen weeks after fracture, roentgenograms showed the alinement in the antero-posterior plane to be very good. The distal fragment was displaced backward about one-half the width of the shaft but without overriding. Clinical union was firm, so traction was removed and a walking caliper splint applied. Flexion of the knee was present through about 25 degrees. The patient was referred to the physical therapy department for intensive treatments. He made slow progress, so that it was necessary on December 15 and Jan. 2, 1928, to manipulate the knee under gas anesthesia. The patient was discharged from the hospital on January 13. He was wearing a caliper splint at all times. There was present moderate atrophy of the entire right lower extremity. Flexion of the knee was present to 75 degrees. On March 3, the caliper splint was discarded. On May 15, the patient returned to work, ten months after injury. Examination showed slight atrophy of muscles of the right thigh. The patient walked without a limp, though measurements showed the right limb to be $\frac{1}{2}$ inch shorter than the left. Motion in the ankle and hip was normal. Flexion of the knee was impaired 15 per cent.

CASE 8.—S. Q., a man, aged 22, was injured on June 1, 1927. He was standing on the edge of a ditch when the walls caved in, so that he fell into the ditch and into the chains of a ditch digger. The following injuries were sustained: (1) fracture of the left femur, (2) fracture of the right tibia and fibula and (3) extensive lacerations of the right forearm. Roentgenograms of the left femur showed a short oblique fracture of the shaft at about the junction of the middle and upper thirds. There was overriding of about 1 inch. A triangular fragment about $2\frac{1}{2}$ inches (6.27 cm.) was detached from the posterior surface of the distal fragment. Russell traction was applied with 8 pounds of weight. Clinical examination on August 3, nine weeks after the fracture, showed firm union, so traction was removed. The roentgenograms showed considerable callus. The ends were in apposition for more than three-fourths of their surface, and alinement was good. On November 25, the patient was bearing full weight on the injured limb. There was complete restoration of function, and he was about ready to resume work when he slipped and fell downstairs, refracturing his left femur. The roentgenograms showed the fracture to be through the newly formed bone. There was marked outward angulation, the distal fragment being displaced inward and posteriorly. There was overriding of about 2 inches. The leg was placed in traction with 8 pounds of weight. Examination on Feb. 1, 1928, nine weeks after fracture, showed firm clinical union. The roentgenograms showed reunion with slight posterior bowing.

The ends were in apposition. There was 35 per cent flexion of the knee. Traction was removed, and the patient was kept in bed. He was allowed to use crutches on March 21, and was referred to the physical therapy department. He was discharged from the hospital on May 15. On July 17, he returned to work, eight months after the second fracture and thirteen months following the original fracture. The limbs were equal in length, and the patient walked without a limp. The muscles of the thigh were not atrophic. Motion of the hip and ankle joints was normal. Flexion of the knee was impaired about 10 per cent.

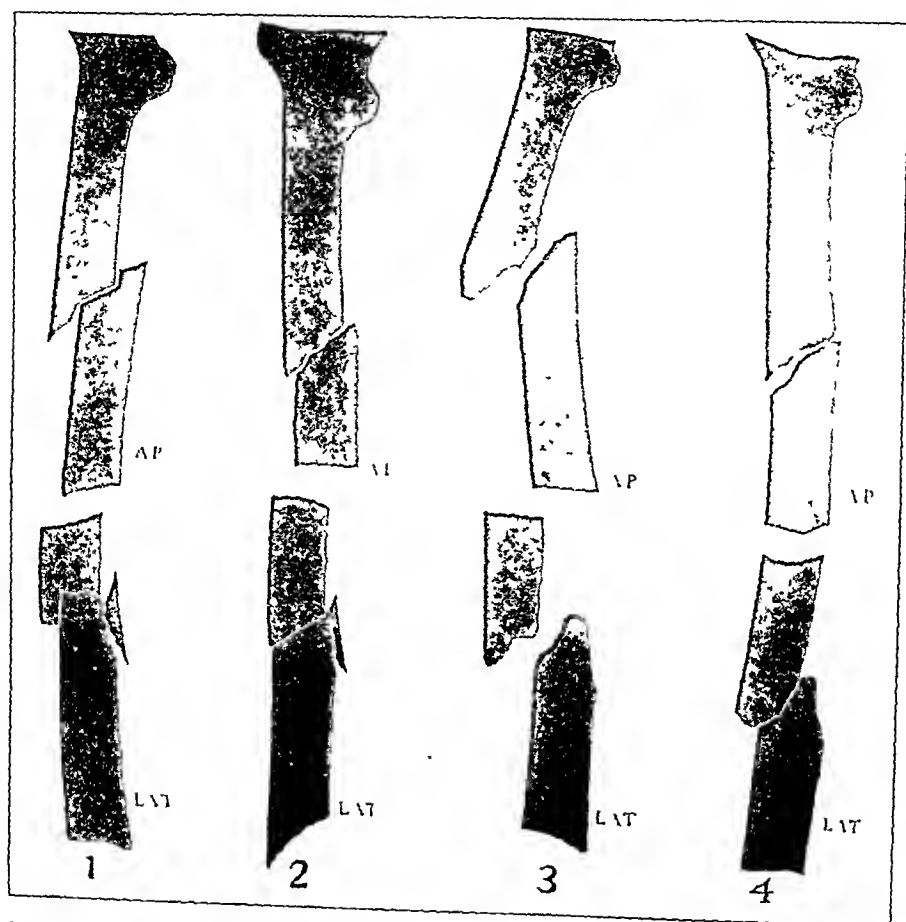


Fig. 9 (case 8).—Roentgenograms taken on: 1, June 1, 1927; 2, Aug. 3, 1927; 3, refracture, Nov. 25, 1927; 4, Feb. 1, 1928.

CASE 9.—G. J., a man, aged 58, was injured on Nov. 13, 1928, when he was struck by an automobile while crossing a street. He was in a state of considerable shock. The roentgenograms showed a long comminuted oblique fracture of the upper third of the shaft of the left femur. The upper fragment was split longitudinally in half, the posterior portion being displaced posteriorly and inward. The lesser trochanter was comminuted and detached. There was overriding of about $1\frac{1}{2}$ inches. The leg was placed in Russell traction with 8 pounds of weight. Convalescence was complicated by myocarditis with partial decompensation and acute retention from a hypertrophied prostatic median lobe. On Jan. 26, 1929, ten weeks after fracture, traction was removed but considerable bending

occurred at the site of the fracture, so traction was reapplied. On April 26, twenty-three weeks after fracture, there was a firm clinical union with good callous formation, so traction was again removed and a caliper splint applied. Roentgenograms taken on May 4 showed no recurrence of deformity, so the patient was allowed to use crutches. Flexion of the knee was 25 per cent normal. On September 26, the caliper splint was discarded. Examination on Jan. 15, 1930, showed perfect clinical union. The patient walked with a slight limp, and measurement of the limbs showed shortening of $\frac{3}{4}$ inch (1.9 cm.). Motion of the ankle was normal. Extension of the knee was normal; flexion was impaired 10 per cent. Flexion of the left hip was 114/130, and extension was normal. Abduction was limited 10 per cent. Adduction and external rotation were normal, while internal rotation was limited 15 per cent. The patient was able to work, but was prevented due to an attack of acute cardiac decompensation.

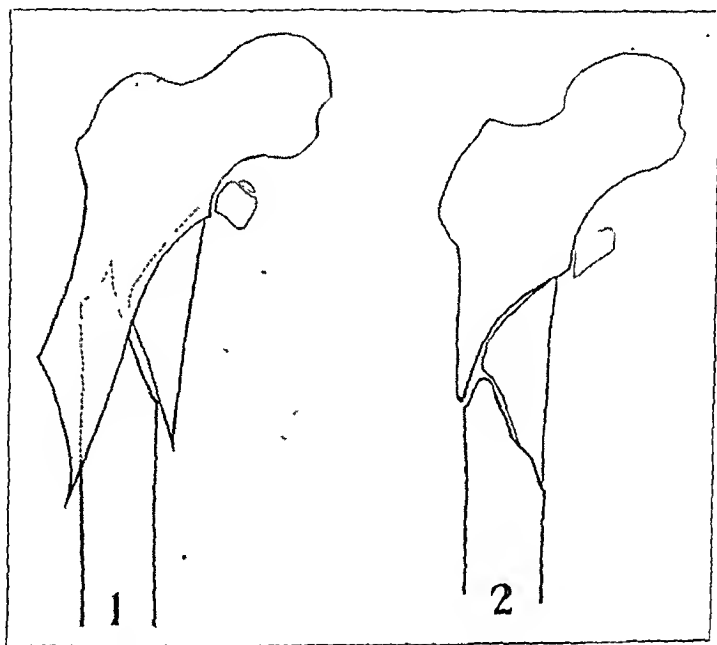


Fig. 10 (case 9).—Roentgenograms taken on: 1, Nov. 13, 1928; 2, Jan. 26, 1929.

CASE 10.—J. E., a man, aged 63, was injured on Nov. 26, 1929, when he was caught in an elevator shaft and dragged to the basement. He sustained a compound fracture of the left femur and a compound fracture of the left humerus. Physical examination showed chronic bronchitis and hypertension with arteriosclerosis. The roentgenograms showed a comminuted fracture of the midportion of shaft of the left femur with overriding of 2 inches. There was a large fragment completely detached from the outer and posterior portion of the shaft. The leg was placed in Russell traction with 8 pounds of weight. Roentgenograms taken on December 26, showed inward angulation which was corrected by outward traction. Examination on Feb. 26, 1930, twelve weeks after injury, showed firm clinical union, so traction was removed and a walking caliper splint applied. The knee showed complete extension with flexion of 50 degrees. Motion of the ankle was normal. The patient was given intensive physical therapy. The caliper splint was discarded on April 28. On May 28, the patient walked with only a cane. He returned to work on August 1, eight months after injury. Examination showed

that he walked without a limp, the limbs measuring the same. There was some muscular atrophy. Motion of the ankle, knee and hip was normal.

CASE 11.—S. P., a man, aged 48, was injured on Aug. 4, 1929, when he slipped on a wet floor, fell and fractured his right thigh. The roentgenograms showed an irregular transverse fracture of the femoral shaft about 6 inches above the knee with complete displacement of the fragments and overriding of $1\frac{1}{2}$ inches. The distal fragment was displaced anteriorly and inward. Russell traction was applied with 8 pounds of weight. Callus was very slow in forming. Examination on December 26 showed evidence of union so that a caliper splint was applied. Five



Fig. 11 (case 10).—Roentgenograms taken on: 1, Nov. 26, 1929; 2, Feb. 26, 1930.

days later the patient began to complain of pain at the site of the fracture, and there was evidence of bowing. Traction was reapplied. Examination on Feb. 18, 1930, twenty-eight weeks after the accident, gave evidence of firm union. The roentgenograms showed good alinement and position with abundant callus. The walking caliper splint was reapplied. Motion of the ankle was normal. Extension of the knee lacked 10 degrees of being normal; flexion was possible through 25 degrees. There was marked muscular atrophy of the right thigh and leg. The patient was given intensive physical therapy. On July 9, the caliper splint was discarded. On August 1, the patient walked with only the aid of a cane. There was no limp, no shortening and only moderate muscular atrophy. Motion of the

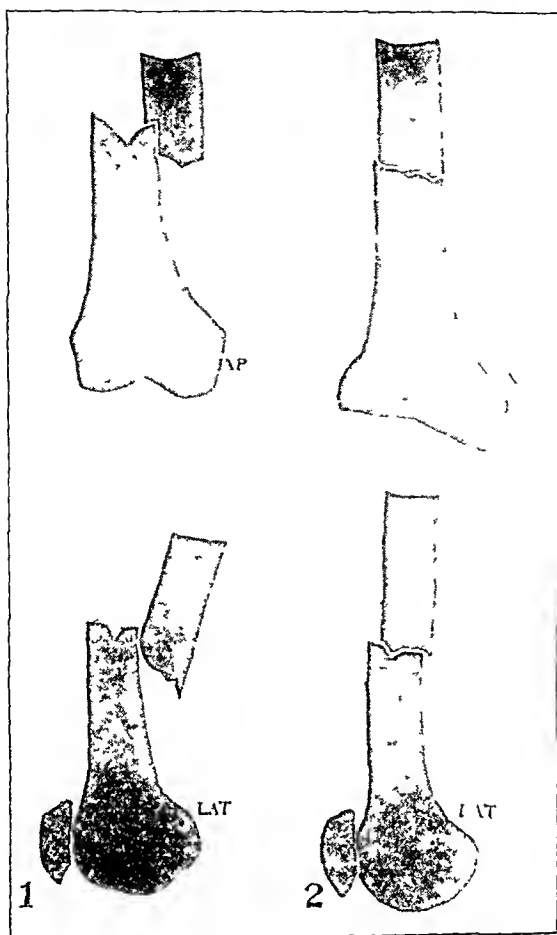


Fig. 12 (case 11).—Roentgenograms taken on: 1, Aug. 4, 1929; 2, Feb. 18, 1930.

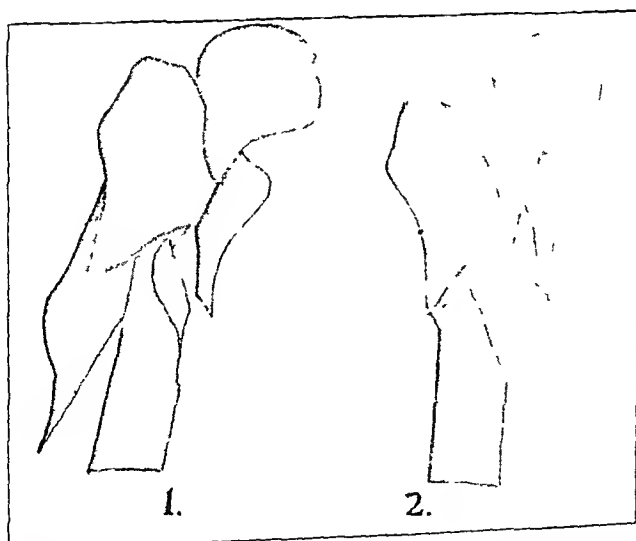


Fig. 13 (case 12).—Roentgenograms taken on: 1, Dec. 31, 1927; 2, Jan. 14, 1928.

ankle and hip was normal. The knee showed complete extension with 15 degrees impairment of flexion. The period of further disability was estimated at two months, making the total period of disability fourteen months.

CASE 12.—J. R., a man, aged 36, was injured on Dec. 31, 1927, when he fell from the top of an ice truck 20 feet to the pavement. He suffered considerable shock. The roentgenograms showed a severely comminuted fracture of the left femoral shaft in the subtrochanteric region. The lesser trochanter was completely separated from the shaft and displaced upward and posteriorly. The fragments were widely separated. External measurements showed 2 inches of shortening. Russell traction was applied with 8 pounds of weight. Roentgenograms taken on Jan. 14, 1928, showed that shortening was only partially overcome and that fragments were still separated, so 3 additional pounds of weight was added. Roentgenograms taken on February 4 showed good alinement and apposition, so the extra weight was removed. On March 23, twelve weeks after injury, examination showed firm union. Traction was removed, and the patient was fitted with a walking caliper splint and allowed to use crutches. On June 28, the caliper splint was discarded. The patient returned to light work on August 16, seven and one-half months after fracture. He complained of occasional pain in the left hip, and walked with a slight limp. Measurements showed about $\frac{3}{4}$ inch of shortening. Extension of the knee was complete with 10 degrees impaired flexion. Flexion of the hip was impaired 20 per cent. Adduction and external rotation were slightly impaired. Other motions were normal.

CASE 13.—J. W., a man, aged 33, was injured on June 9, 1929, when a large rock which was thrown into the air from an explosion fell on his left thigh, causing a compound fracture of the left femur. The roentgenograms showed a transverse fracture of the shaft at the junction of the middle and lower thirds with overriding of about 3 inches (7.6 cm.). The distal fragment was displaced posteriorly. Russell traction was applied with 8 pounds of weight. The wound in the thigh healed without infection. On June 26, the fracture was not reduced, the distal fragment remaining displaced posteriorly. On June 27, skeletal traction was applied to a Steinman nail which was passed through the upper part of the tibial shaft. Roentgenograms taken on July 28 showed good alinement and position anteroposteriorly but complete displacement posteriorly. There was no sign of callus formation. An open reduction was performed, and a band of muscle the thickness of one's palm was found interposed between the fragments. An intramedullary peg was inserted, and a body plaster cast applied.

CASE 14.—J. B., a man, aged 24, was injured on June 24, 1929, when a heavy piece of lumber was "kicked back" by a rip saw and struck his right thigh. He suffered moderate shock. The roentgenograms showed a comminuted fracture of the shaft of the right femur at the junction of the middle and lower thirds. There was overriding of about 2 inches. The leg was manipulated without anesthesia and placed in Russell traction with 8 pounds of weight. Roentgenograms taken on July 24, in the anteroposterior plane, showed good position and alinement. Lateral views showed continued posterior displacement of the distal fragment with about $\frac{3}{4}$ inch of overriding. There was a fair amount of callous formation. Callus continued to form, but no union occurred. The case was considered one of delayed union. The patient was given calcium and viosterol. On December 11, as there was no union, an open operation was performed. A large band of muscle fibers was found between the ends of the bone. This band was liberated, and an intramedullary inlay placed. Recovery was uneventful.

CASE 15.—J. C., a man, aged 39, was injured on June 4, 1928, when a derrick on which he was working collapsed and he fell 20 feet to the ground. Examination showed a fracture of the left femur and fracture of the left ninth and tenth ribs. The roentgenograms showed a markedly comminuted pertrochanteric fracture, the main line of fracture running obliquely from a mesial point just above the lesser trochanter to the outer side of the shaft below the greater trochanter. The lesser trochanter was completely detached and comminuted. There was a secondary line of fracture running longitudinally through the greater trochanter. There was a marked coxa vara deformity. Measurements showed the leg to be shortened $2\frac{1}{2}$ inches. Russell traction was applied with 8 pounds of weight. Examination on August 24, eleven and one-half weeks after injury, showed firm clinical union, so traction was removed. The roentgenograms showed good alignment and position with bony union. A caliper splint was applied, and the patient was given physical therapy. On Jan. 9, 1929, he discarded the caliper splint. On March 1, nine months after injury, he returned to work. He walked with a slight limp. Measurements showed $\frac{1}{2}$ inch of shortening. Motion in the left hip was

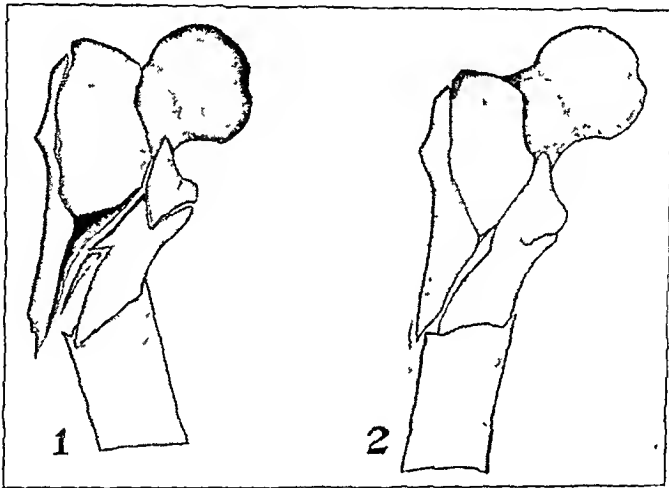


Fig. 14 (case 15).—Roentgenograms taken on: 1, June 4, 1928; 2, Aug. 24, 1928.

normal, except for 50 per cent impairment of internal rotation. The left knee showed complete extension with 10 per cent impaired flexion. Motion of the ankle was normal.

CASE 16.—K. K., a man, aged 34, was injured on March 12, 1929, when some 125 pound (56.7 Kg.) sacks of potatoes fell on his left thigh. He sustained a fracture of the left femur. He was taken to another hospital where he was treated by traction for ten days without success. Open operation was done on March 21, a Lane plate being used. A cast was applied; it was removed on April 25, and the patient was allowed to use crutches. Increasing deformity resulted. He was transferred to the Golden State Hospital on May 14. The roentgenograms showed an old transverse subtrochanteric fracture of the left femur. The fragments were in end-to-end position, but there was marked outward and backward bowing. The Lane plate was present, but the screws were pulled loose. There was a fair amount of callus. Measurements showed 1 inch of shortening. Traction was applied with 8 pounds of weight. Examination on June 24 showed firm union, so traction was removed. Roentgenograms showed good alignment and position. Measurements of both legs showed equal length. Motion of the ankle was normal. The knee

showed full extension, with 20 per cent impaired flexion. The patient was referred to the physical therapy department. He began weight-bearing on August 8. He returned to work on Jan. 1, 1930, nine and one-half months after the accident. There was slight atrophy of the muscles. Measurements of the legs showed equal length. Motion of the hip, knee and ankle was normal.

CASE 17.—G. M., a man, aged 57, was injured on Aug. 27, 1928, when he fell from a ladder 7 feet to a concrete floor. He sustained a fracture of his right femur. The roentgenograms showed an intertrochanteric fracture with impaction near the base of the lesser trochanter and formation of moderate coxa vara. The inferior and posterior portion of the lesser trochanter was avulsed. External measurements showed 1 inch of shortening. Russell traction was applied. Examination on October 23, nine weeks after injury, showed firm clinical union, so traction was removed. Roentgenograms revealed apparent bony union. At the end of ten days, roentgenograms revealed no recurrence of the deformity, so the patient was allowed to use crutches but he was not permitted to bear weight. He returned to work on April 1, 1929, eight months after injury. Examination showed that he walked with a limp, although measurements showed equal length of the legs. Slight muscular atrophy was present. Motion of the knee and ankle was normal. Internal rotation of the hip was impaired 20 per cent, with 20 per cent impaired flexion.

CASE 18.—M. N., a man, aged 65, was injured on Dec. 5, 1929, when some scaffolding on which he was standing broke and he fell 14 feet to the pavement. He sustained a fracture of the right thigh and right forearm. The roentgenograms showed a pertrochanteric fracture of the femur with the greater trochanter avulsed and displaced slightly posteriorly. The line of fracture extended downward through the center of the shaft for a distance of about 1 inch beyond the lesser trochanter. There was moderate impaction of the fracture with slight external rotation of the distal fragment and varus deformity. Measurements showed 1 inch of shortening. Russell traction was applied with 8 pounds of weight. Examination on March 1 showed firm clinical union. The roentgenograms showed apparent bony union. Traction was removed, and the patient was allowed to remain in bed. Roentgenograms taken at the end of ten days showed no recurrence of the deformity, so the patient was allowed to use crutches but was not allowed to bear weight. Measurements showed the right leg to be 35 inches in length, and the left, 35¼ inches. Motion of the ankle was normal. Extension of the knee was complete, with flexion of 113/127. On August 1, the patient was bearing weight on his foot. The hip showed 40 per cent impairment of flexion with moderate impairment of internal rotation. Motion of the knee was practically normal; that of the ankle, normal. Measurements showed ¼ inch of shortening. Further disability was estimated at from three to four months, the total period of disability from the time of injury being about one year.

CASE 19.—J. B., a man, aged 52, was injured on April 1, 1929, when he fell through an opening in a floor about 20 feet, landing on the pavement. The roentgenograms showed an intertrochanteric fracture of the left femur. There was moderate separation of the line of fracture at the upper margin of the greater trochanter with impaction near the base of the lesser trochanter. There was considerable inward displacement of the entire shaft with the production of moderate coxa vara deformity. Measurements showed 1½ inches of shortening. Russell traction was applied with 8 pounds of weight. Examination on June 10, nine weeks after the accident, showed firm union. The roentgenograms showed

excellent position and alinement with evidence of bony union. Traction was removed. The patient remained in bed until June 24, when roentgenograms showed no recurrence of the deformity. He was allowed to use crutches and was referred for physical therapy. Roentgenograms taken July 15, showed complete obliteration of the line of fracture. The patient began to bear weight in August, 1929. He discarded his crutches on October 15, and was able to return to work on Feb. 1, 1930, ten months after the accident. Examination showed the limbs to be equal in length, the patient walking without a limp. Function of the knee and ankle joints was normal. There was slight limitation of internal rotation and flexion of the hip, but no apparent muscular atrophy.

CASE 20.—A. V., a woman, aged 73, was injured on Oct. 15, 1929, when she fell in the dark over a chair and struck her left hip on the floor. She was immediately disabled and lapsed into a state of profound shock. The roentgenograms showed an impacted avulsion fracture of the greater trochanter of the left femur and an oblique intertrochanteric fracture with the fracture line extending into the shaft of the femur for 1 inch beyond the lesser trochanter. The shaft rotated externally. Measurements showed $\frac{3}{4}$ inch of shortening. Russell traction was applied with 8 pounds of weight. Roentgenograms taken on October 20 showed an improvement of position and alinement. Measurements of both extremities were equal. The patient, however, failed to rally; she died on November 9.

CASE 21.—A. D., a woman, aged 60, was injured on March 10, 1930, when an automobile in which she was riding turned over as a result of a blowout of a tire. She was taken to a nearby hospital where temporary splints were applied; then she was transferred by ambulance to the California Hospital, Los Angeles. Examination showed marked deformity, swelling and false motion at the junction of the middle and upper thirds of the left thigh. There was $1\frac{3}{4}$ inches of shortening. The patient was suffering from chronic bronchitis. Roentgenograms taken March 11 showed: (1) a markedly comminuted fracture of the upper third of the left femur with complete displacement (the upper fragment was displaced inward and posteriorly) and (2) transverse fracture of the lower one third of the left femur with slight inward and posterior displacement.

Temporary splints were used until March 15, when the patient was transferred to her home, where the limb was placed in Russell traction with 8 pounds of weight. Clinical examination on May 29, eleven and one-half weeks after injury, showed firm union, so traction was removed. Motion of the ankle was normal. Extension of the knee was complete; there was 80 degrees of flexion. The patella was free. Measurements showed $\frac{1}{4}$ inch of shortening. On June 10, the patient was allowed up in a wheel chair, no recurrence of deformity having occurred. She was given crutches on June 21, and began light weight-bearing. Flexion of the knee was 112 degrees. On July 12, she walked with one crutch and cane. There was no pain at the site of the fracture. Flexion of the knee was 120 degrees. On August 1, about five months after injury, the patient was walking without support and doing regular housework. Motion of the ankle, knee and hip was practically normal. There was slight edema of the leg and ankle. The left limb was $\frac{1}{4}$ inch short, but the patient walked without a limp.

CASE 22.—E. B., a man, aged 21, was injured on Aug. 12, 1930, when he slipped from the roof of a four story building and fell to the ground. He sustained fractures of both wrists, fracture of the transverse processes of the first and second lumbar vertebrae, together with a fracture of the left femur. Examination of the femur showed deformity, loss of function and acute tenderness to pres-

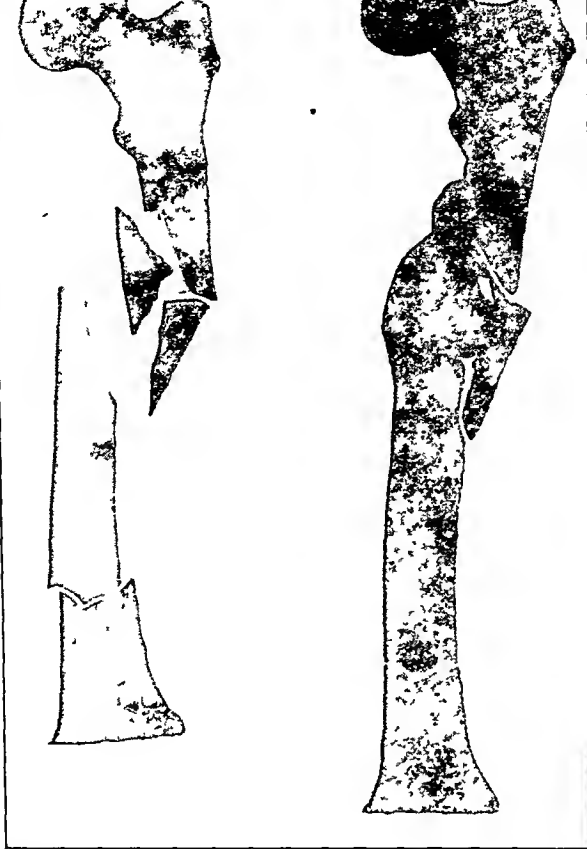


Fig. 15 (case 21).—Roentgenograms taken on March 11 and June 21, 1930, respectively.

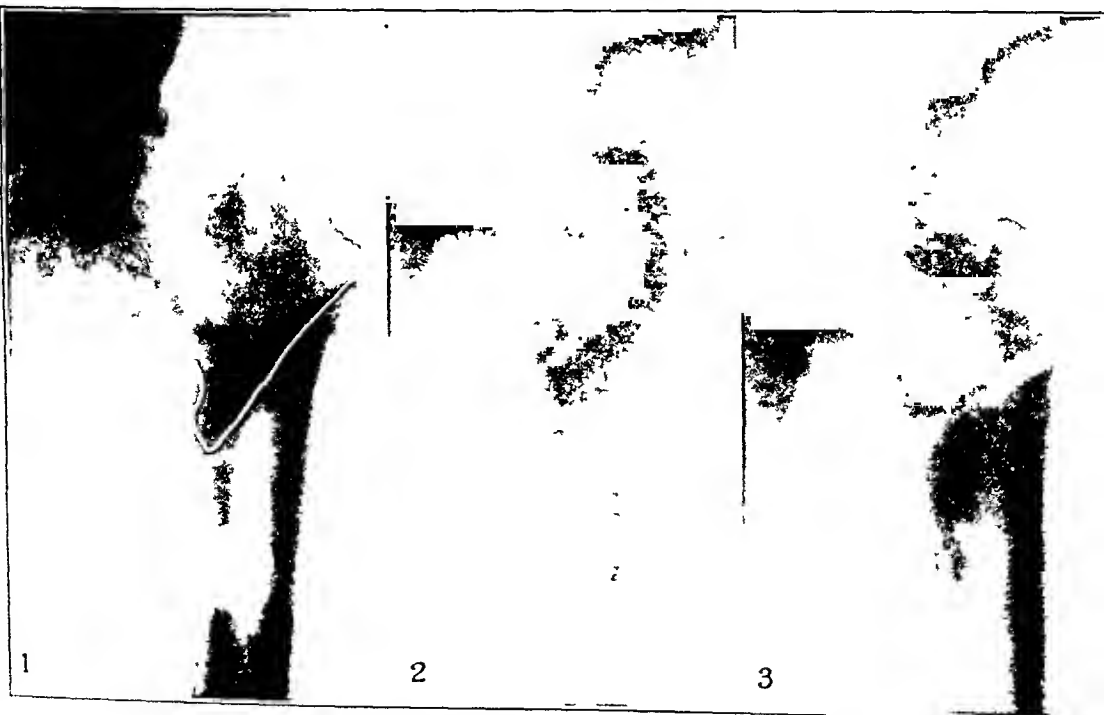


Fig. 16 (case 22) —Roentgenograms taken on: 1. Aug. 12, 1930, showing degree of impaction; 2. August 15, showing reduction of impaction with outward and upward displacement of the proximal fragment; 3. August 16, showing almost perfect position and alinement.

sure in the region of the greater tuberosity. The greater tuberosity moved with the femur on rotation, and no crepitus was obtained. Measurements showed $1\frac{1}{2}$ inches of shortening. Roentgenograms taken on August 12, showed a complete transverse pertrochanteric fracture of the left femur. The upper fragment was impacted into the lower. There was moderate diminution of the angle between the neck and the shaft. The patient was congenitally syphilitic.

Russell traction was applied with 8 pounds of weight with the limb in about 10 degrees of abduction. Roentgenograms taken on August 15 showed that the impaction had been entirely reduced. There was considerable outward and upward displacement of the proximal fragment. The limb was placed in 40 degrees abduction, the same amount of weight being used. Roentgenograms taken on August 16 showed almost perfect position and alinement.

Two patients with fractures of the acetabulum were treated by the Russell method, 6 pounds of weight being used; excellent results were obtained. This method was also employed on a child, aged 5, who had sustained a complete fracture of the left innominate bone with marked upward dislocation. Four pounds of weight was used, the dislocation was overcome, and a perfect result was obtained.

COMMENT

Twenty-one cases of fracture of the femur are reported. In case 3, a fracture of both femora was sustained; in case 21 a double fracture of the femur, so that the total number of fractures treated were twenty-three. Ridgely and Bongardt³ reported the successful treatment of intracapsular fractures of the neck of the femur by this method, also epiphyseal separation of the lower end of the femur. Ryan² stated that the method is ideal for elderly patients who have sustained a fracture of the neck of the femur and in whom the Whitman reduction is not advisable.

Intertrochanteric Fracture.—Three patients with intertrochanteric fracture were treated, all over 50 years of age. The only mortality occurred in this group. The line of fracture followed the anterior oblique line, connecting the two trochanters. There was moderate impaction, the displacement consisting in flattening of the angle made by the neck of the shaft and resulting in the production of a coxa vara deformity.

The average period of traction was nine weeks, with hospitalization of twelve and one-half weeks. It was not necessary for the patients to wear supporting caliper splints. They began to bear weight four months after injury. The average period of disability was nine months. The limbs were equal in length. Slight muscular atrophy was present.

3. Ridgely, I. O., and Bongardt, H. F.: Treatment of Fractures of the Femur by the Hamilton Russell Method Traction, *Am. J. Surg.* 7:251 (Aug.) 1929.

Motion in the ankle and knee joints was normal. In one case, there was slight limitation of internal rotation and flexion at the hip.

Pertrochanteric Fractures.—Two patients with pertrochanteric fractures were treated. The line of fracture passed more or less transversely across the upper end of the femoral shaft, beginning on the mesial side above the lesser trochanter and terminating on the outer side below the great trochanter. The lesser trochanter was either attached to the distal fragment or was torn loose and formed a third fragment. Comminution was present, with moderate coxa vara deformity. In those cases in which the lesser trochanter is fractured and displaced, the Russell method is ideal, as the limb can be immobilized in a position of flexion and slight internal rotation, and relaxation of the detached ileopsoas muscle thereby obtained.

TABLE 4.—Results in Cases of Intertrochanteric Fracture

Case	Age	Traction	Hospital	Disability
17	57	9 weeks	12 weeks	8 months
19	52	9 weeks	13 weeks	10 months
20	74	Fatal		

TABLE 5.—Results in Cases of Pertrochanteric Fracture

Case	Age	Traction	Hospital	Disability
15	39	11½ weeks	14½ weeks	9 months
18	65	12 weeks	16 weeks	12 months

The average period of traction was twelve weeks, with hospitalization of fifteen weeks. Disability extended for ten and one-half months. The resulting shortening was $\frac{1}{2}$ and $\frac{1}{4}$ inches, respectively. In both cases there was some limitation in the motion of the hip. Case 15, in which the lesser trochanter was separated from the shaft, showed an approximate 50 per cent loss of internal rotation. In this case there was severe comminution, and a caliper splint was used for four months after traction was removed.

Fractures of Proximal End Shaft of Femur.—Seven patients with this type of fracture were treated. In the majority of cases, the short proximal fragment was flexed and externally rotated. Those of the subtrochanteric type also showed some abduction. The longer distal fragment lay posteriorly and was drawn downward. The Russell type of traction tends to overcome the shortening and to lift the distal fragment and bring it into proper relation with the proximal one. If the upper fragment is abducted, the entire limb may be swung into abduction as well as being flexed and extended. A direct pull without abduction, however, tends to give the maximum restoration of alinement.

It was possible to reduce all these fractures. The average period of traction was twelve weeks; of hospitalization, fifteen weeks, and of disability, nine months. Healing was prolonged in case 5 due to a syphilitic infection. In case 9 there was severe comminution, and convalescence was prolonged by cardiac and renal disease. In three cases it was necessary to give added support with a caliper splint after traction was removed. Four cases showed some shortening—two $\frac{3}{4}$ inch and two $\frac{1}{4}$ inch. Motion of the ankle was normal. Case 9 showed 10 per cent loss of flexion of the knee due to prolonged immobilization together with interference of normal quadriceps function by the formation of new bone at the site of the fracture. In the same case there was con-

TABLE 6.—*Results in Cases of Fracture of the Proximal End of the Femur*

Case	Age	Traction	Hospital	Disability
1	17	9½ weeks	12 weeks	9 months
3	19	8 weeks	10 weeks	6 months
5	31	14 weeks	16 weeks	9 months
9	58	23 weeks	26 weeks	14 months
12	36	12 weeks	15 weeks	7½ months
16	34	6 weeks	10 weeks	9½ months
21	60	11½ weeks	Home	5 months

TABLE 7.—*Results in Cases of Fracture of the Middle Third of the Femur*

Case	Age	Traction	Hospital	Disability
2	54	9 weeks	12 weeks	7½ months
3	19	8 weeks	10 weeks	6 months
6	19	8 weeks	9 weeks	5½ months
7	25	13 weeks	16 weeks	10 months
8	22	9 weeks	12 weeks	9 months
10	63	12 weeks	14 weeks	8 months
14	24	Unable to reduce		

siderable stiffness at the hip joint, where the lesser trochanter had been comminuted and detached.

Fractures of the Middle Third of the Shaft of the Femur.—Seven patients with this type of fracture were treated. The displacement here did not depend as much on the muscular action as on the direction and action of the fracturing force. The distal fragment was usually posterior to the upper one. Outward angulation was seen when the ends of the fracture remained in apposition; inward displacement of the lower fragment was seen when the ends had slipped by. Indications for the traction method here were to overcome shortening and to apply side traction if lateral angulation was present. This group showed a disposition toward posterior sagging at the site of fracture.

In one of these cases it was not possible to reduce the fracture, and subsequent open operation showed interposition of muscles between the fractured ends. The average period of traction was nine weeks, with

twelve weeks of hospitalization. The period of disability averaged seven and one-half months. It was necessary for three of the patients to wear calipers for two and one-half months after the traction was removed. Two cases resulted in $\frac{1}{2}$ inch of shortening. In three cases there was slight residual impairment of flexion of the knee, the maximum being 15 degrees in case 7 in which the period of immobilization was prolonged. Motion of the hip and ankle was normal.

Fractures of the Distal End of the Femur.—Four patients with this type of fracture were treated. The lower fragment here was tilted posteriorly by the action of the gastrocnemius. The distal end of the upper fragment showed a tendency to pass downward and forward toward the patella. None of the patients showed injury to the popliteal vessels, but one did show injury to the external popliteal nerve, as evidenced by inability to dorsiflex the foot or extend the toes, together with numbness over the dorsum of the leg. The Russell method in

TABLE 8.—*Results in Cases of Fracture of the Distal Third of the Femur*

Case	Age	Traction	Hospital	Disability
4	18	11 weeks	14 weeks	8 months
11	48	28 weeks	31 weeks	14 months
13	33	Unable to reduce		
21	60	11½ weeks	Home	5 months

these types of fractures overcomes the shortening and tends to correct the backward rocking of the lower fragment by flexion of the knee, thereby relaxing the gastrocnemius muscles.

In one of these cases the fracture was not reduced, owing to the interference of soft tissues. Case 4 resulted in $\frac{1}{2}$ inch of shortening, but with normal function. In case 11 union was delayed, but normal function without shortening resulted.

The average amount of weight used in the reduction was 8 pounds, this being sufficient except in two cases in which it was necessary to add 3 pounds. In four cases side traction with 3 pounds was applied to overcome inward bowing. Posterior bowing was successfully prevented in all cases by the use of a soft pillow, which was placed immediately under the thigh at the site of fracture.

The duration of traction for all types of fractures of the femur averaged nine weeks, the shortest was eight weeks. Two cases of delayed union were seen in which firm clinical healing did not take place until after twenty-three and twenty-eight weeks, respectively. Both of these patients were treated with calcium and viosterol. In one case that was complicated by a syphilitic infection, antisyphilitic treatment was given and firm union occurred after fourteen weeks.

In three cases there appeared to be firm clinical union at the time of removal of the traction. These patients were allowed to move about freely in bed, but after a few days, they began to complain of pain and tenderness at the site of fracture. The roentgenograms showed a beginning recurrence of angulation, and traction was reapplied. One of these cases was complicated with syphilis; the other two showed delayed union.

The average period of hospitalization was twelve weeks; the shortest nine weeks, and the longest thirty-two weeks.

In eight cases it was thought advisable that the patient wear a walking caliper splint. These were cases in which there was delayed union or a severe comminution or in which the roentgenograms showed a relatively small amount of callus. The calipers were worn on an average of two and one-half months.

The average period of temporary disability was nine months; the shortest period five and one-half months, the longest fourteen months.

In evaluating the results obtained by this method, the triad of contour, union and function has been taken into consideration.

Contour in all cases was normal. There was no apparent bowing. One case showed a slight prominence over the dorsum of the thigh at the site of fracture, which was due to the formation of excessive callus. The muscles in two cases were somewhat atrophied. There was no apparent shortening, although in two of the cases the patients walked with a slight limp.

Union was obtained in all but two cases. Subsequent open operation showed that in both of these cases muscle tissue was interposed between the ends of the fracture. Firm clinical union usually occurred at from eight to ten weeks. No cases of fibrous union were encountered, though two were rather delayed in forming hardened callus.

Function in all cases was good. Five cases, one of them with a fracture of both femoral shafts, showed a return to absolute normal. There was no shortening in nine cases; two cases showed $\frac{1}{4}$ inch of shortening, four cases $\frac{1}{2}$ inch and two cases $\frac{3}{4}$ inch. Motion of the ankle was normal in all cases. The knee showed complete extension in all cases. Flexion was somewhat impaired in six cases, the maximum amount being 15 degrees. Motion of the hip was normal in all but four cases, in which some impairment of internal rotation and flexion resulted. All of these patients had sustained severely comminuted fractures of the lesser trochanter with partial separation.

SUMMARY AND CONCLUSIONS

I have used practically all recognized methods of treatment in cases of fracture of the femur. I have obtained the best results by the use of the Russell traction apparatus. This method depends on a natural and

comfortable position of the limb with a minimum of weight whereby the equilibrium of the muscle is restored; with this restoration of muscle tone and position, the fractured ends of the bone will fall into a more or less natural alinement, provided there is no interposed tissue. One must bear in mind that an absolute restoration of anatomic position is not necessary for a good functional result. I have used the method as described by Russell with practically no change. The apparatus, its application and the after-care of the patient have been described. The results have been analyzed and the following deductions drawn:

1. The Russell method of traction is the method of choice in treating all types of fractures of the femur from the intertrochanteric to the lower epiphyseal regions.

2. It gives satisfactory position and alinement in all cases, except when muscle is interposed between the fractured ends.

3. It gives a minimum of permanent changes in the joint as compared with other methods.

4. The average period of traction in fractures of the femur is nine weeks, of hospitalization twelve weeks and of temporary disability nine months.

5. The method is inexpensive, easy to apply, comfortable to the patient and materially simplifies nursing care.

PAGET'S DISEASE

A PREDISPOSING FACTOR TO OSTEOGENIC SARCOMA *

BRADLEY L. COLEY, M.D.

AND

GEORGE S. SHARP, M.D.

NEW YORK

The frequent association of Paget's disease and osteogenic sarcoma in patients over 50 years of age has attracted the attention of other observers. Our interest was aroused because of three cases recently coming under our observation, and a careful study of the subject was undertaken. We would reiterate Codman's¹ suggestion that such cases deserve a separate division in the Registry classification because of their different clinical features. It seems to us also that this group may be important in giving a clue to one of the etiologic factors of osteogenic sarcoma. We know of no instance of the development of a benign giant cell tumor or endothelial myeloma occurring in a bone that was the site of a preexisting Paget's disease.

For a clear understanding of the problem, it has seemed advisable to summarize briefly some of the known facts concerning Paget's disease.

DESCRIPTION OF OSTEITIS DEFORMANS

Sir James Paget,² in 1877, first described the disease that bears his name. It is apparent that it is a constitutional disease, although it may manifest itself in a single bone; it more commonly involves a number of bones, and of these the skull is a favorite site. The condition is considered rare, although most writers agree that it probably occurs more frequently than is generally recognized, for it seems likely that it is often overlooked, especially when it attacks only the skull.

ETIOLOGY

While its etiology is still unexplained, numerous theories have been advanced. Arterial changes in the vessels of the extremities are often found, but as the disease occurs in persons of advancing years, this symptom may be of little significance. Probably the most engaging theory is that it is due to a defective metabolism of calcium, having as

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* From the Department of Bone Tumors, Memorial Hospital.

1. Codman, E. A.: Personal communication.

2. Paget, James: *M. Chir. Tr.* **60**:37, 1877; *Illust. M. News* **2**:181, 1889.

its underlying basis a faulty function of the parathyroid glands. Much recent work has tended to show that cases of von Recklinghausen's disease (osteitis fibrosa cystica) are associated with a high rate of excretion of calcium, and in a number of instances abnormal changes have been noted in the parathyroid glands. The similarity, in many respects, of Paget's and von Recklinghausen's diseases leads one to the view that both may have their origin in some disorder of the parathyroids as yet little understood. Further investigation is needed along these lines and may be productive of real information; moreover, it is not beyond the bounds of reasonable hope that endocrine therapy may offer something of value in the treatment for osteitis deformans, an achievement not hitherto attained.

GROSS APPEARANCE

The changes in the bone seen in Paget's disease are characteristic and are the result of a combination of destruction of bone and formation of new bone. The latter, however, does not consist of normal bone, but of osteoid tissue. Changes in the shape, size and structure of the bone occur. The medullary cavity is encroached on, and in advanced cases it is often impossible to state where the cortex ends and the medulla begins. The skull, spine and the long bones of the lower extremity are most frequently affected. The microscopic pathology will be considered in some detail when the association with osteogenic sarcoma is discussed.

SYMPTOMS AND SIGNS

Bowing of the lower extremities occurs, due to the effect of the bearing of weight, and the resulting deformity is one of the characteristic features of the disease. In other cases, however, the increase in the size of the head is the first symptom noted. Pain in the legs is an inconstant and often transitory symptom; it may disappear entirely as the disease progresses. Fractures sometimes occur in bones affected by the changes of Paget's disease, but union generally results. One of us has observed two cases in which there were fractures of the tibia and one case showing fracture of the humerus, with healing in each instance.

DIAGNOSIS

The diagnosis is not difficult if the condition is suspected and roentgenograms are made, because the changes in the bone as revealed by x-ray films are rather characteristic. Occasional cases of metastasis to bone from carcinoma are seen in which the picture of Paget's disease is closely simulated; of these, prostatic carcinoma is apt to be the most confusing. In the absence of a demonstrable primary growth

elsewhere, the diagnosis of Paget's disease is rendered more certain. While typical cases of osteitis deformans are readily distinguishable from typical cases of osteitis fibrosa cystica, there are certain borderline cases in which the distinction may be difficult. Roentgenograms of a typical case of osteitis deformans showed marked osteosclerosis and osteoporosis in adjacent areas. The degree of osteosclerosis that follows the porosis varies considerably in individual cases.

Garland³ concluded that the two conditions are histologically and anatomically identical. While this may be true, when one analyzes the histogenetic process involved, one finds that in both instances there is a fibrous proliferation with formation of new bone and, therefore, a process of repair or healing. These factors seriously attack the claim of osteitis fibrosa to consideration as a pathologic entity. This same process is also found about the walls of abscesses, bits of capsule from central sarcoma of bone, or secondary metastatic tumors and periosteum overlying ossifying hematoma, which further emphasizes it as a process of repair or a defensive reaction of both cancellous and cortical bone, as well as of the periosteum. The persistence of cystic formations both in Paget's disease and in osteitis fibrosa cystica (single and multiple cysts of the bone) is due to the difficulty that nature has in collapsing a cavity with rigid walls.

While the etiology of Paget's disease is unknown, there is certainly a different process at work in this disease than that in osteitis fibrosa cystica. In 2 per cent of the cysts of the bone, the destructive process of the bone was found to be stimulated by foreign bodies; in 20 per cent, rather loosely classed as osteitis fibrosa, some primary disease such as osteomalacia, fragilitas ossium or disturbances of the parathyroid gland with rarefaction and the formation of cysts in the bones has been responsible for the reaction of the bone. In 78 per cent, representing solitary cysts of the bone, a definite relation has been established between cyst of the bone and giant cell tumor. (These figures are supplied by Dr. Copeland from records at Bloodgood's Clinic.)

Osteitis deformans occurs in patients who have reached middle or late life and presents an entirely different prognosis and response to treatment than that presented by osteitis fibrosa cystica, which occurs for the most part before the twentieth year, frequently shows spontaneous remissions and is often cured by pathologic fracture or surgical intervention. Paget's disease is progressive and up to the present time has been found unresponsive to any form of treatment.

3. Garland, L. H.: *Am. J. Roentgenol.* **22**:517 (Dec.) 1929.

It is our belief that if roentgenograms of the skull were made more generally of patients over 50 years of age it would be found that osteitis deformans is much less rare than it is thought to be. We now make it a practice to obtain films of the skull on all patients in the Bone Tumor Clinic over the age of 50. As mentioned previously, there has as yet been no accepted specific treatment for Paget's disease.

PAGET'S DISEASE ASSOCIATED WITH SARCOMA OF THE BONE

In his earliest communication concerning the disease that bears his name, Paget mentioned the tendency in patients with osteitis deformans to develop neoplastic conditions. In his twenty-three personally observed cases, we learn from a subsequent report that of the eight patients who were traced to their deaths, malignant diseases developed in no less than five.

Delafield⁴ maintained that the incidence of sarcoma among patients with Paget's disease is no greater than in any group of persons of the same age. This is contrary to the opinions of the majority of observers and it seems to be now firmly established that, at least as regards the occurrence of osteogenic sarcoma, Paget's disease is a predisposing factor.

Packard, Steele and Kirkbride⁵ reviewed the literature up to 1901 and collected 66 cases of undoubted osteitis deformans in which there was an associated sarcoma in 5, or 7.5 per cent. DaCosta,⁶ in 1914, assembled 213 cases in which sarcomatous diseases of some form developed in 9.5 per cent. Gruner, Scrimger and Foster⁷ reported that in about 9 per cent of their cases of Paget's disease this condition was associated with sarcoma.

When a condition as relatively rare as Paget's disease comes to be associated with a second condition as uncommon as osteogenic sarcoma, one cannot but seriously consider that this association is more than one of mere chance or coincidence. In one year Camp⁸ observed 2 cases of sarcoma in Paget's disease at the Massachusetts General Hospital. Locke⁹ found that 4 of his 65 patients with osteitis deformans had osteosarcoma or fibrosarcoma (6.2 per cent).

4. Delafield, in Delafield and Prudden: *Textbook of Pathology*, ed. 14, New York, William Wood & Company, 1927, p. 447.

5. Packard, F. A.; Steele, J. D., and Kirkbride, J. S.: *Am. J. M. Sc.* **122**: 252, 1901.

6. DaCosta, J. C.; Funk, E. H.; Bergeim, O., and Hawk, P. B.: *Pub. Jefferson M. Coll. & Hosp.* **6**:1, 1915.

7. Gruner, O. C.; Scrimger, F. A. C., and Foster, L. S.: *Arch. Int. Med.* **9**:641 (June) 1912.

8. Camp, J. D.: *Radiology* **5**:495 (Dec.) 1925.

9. Locke, E. A., quoted by Bird: *Personal communication*.

Bird¹⁰ studied the records of four large Boston hospitals with some interesting results. He was able to collect records of 64 patients with osteitis deformans, in 7 of whom (approximately 11 per cent) sarcoma occurred. He estimated that there is 1 case of Paget's disease in every 15,000 admissions to hospitals in Boston. This corresponds closely with the report¹¹ of 1 in 10,000 at the Johns Hopkins Hospital; 1 in 13,000 at Jefferson⁶ Hospital, and 1 in 16,000 at the Mayo Clinic.¹² At the Peter Bent Brigham Hospital there were 15 cases of osteitis deformans in 45,000 admissions, or 1 in 3,000. This, Bird explained on the theory that a far larger percentage of patients in that hospital had roentgenograms taken (89 per cent). The disease is probably not as rare as the figures from the various hospitals would suggest. In the first place, many patients do not enter hospitals unless some complication arises and even then they may be classified on the records of the hospital according to the complication and not be indexed as having Paget's disease. Moreover, as Bird stated, early examples of the disease are being constantly overlooked, especially when it is confined to 1 bone.

Of the 9 cases of Paget's disease in which there was an accompanying sarcoma, Bird stated that 8 were fatal, the remaining case being untraced. The average duration of life after the first evidence of sarcoma was eight months; the shortest, two and a half months, and the longest one year. In 5 of these 9 cases, there was pathologic verification in the diagnosis of sarcoma. The duration of the Paget's disease prior to the development of sarcoma is mentioned in 6 of the 9 cases. In 1 case, the period was three years; in another, ten; in another, eleven; in 2 cases, fifteen years, and in 1 instance, twenty years.

An interesting report of a case (Cabot,¹³ case 12513) is that of a man, aged 43, with a history of pneumonia eight years before admission, followed by a painful condition of the left leg, which was noted during convalescence. A few months prior to admission the pain increased in severity. There had been an associated decline in the general health of the patient during the last few years. He was admitted with a transverse fracture of the distal portion of the neck of the left femur, which occurred while he was at work, but without any history of violence, either direct or indirect. The Wassermann reaction was negative. Roentgen examination showed evidence of osteitis deformans in

10. Bird, C. E.: Sarcoma Complicating Paget's Disease of Bone; Report of Nine Cases, Five with Pathologic Verification, *Arch. Surg.* **14**:1187 (June) 1927.

11. Hurwitz, S. H.: *Bull. Johns Hopkins Hosp.* **24**:263, 1913.

12. Carman, R. D., and Carrick, W. M.: *J. Radiol.* **2**:7 (April) 1921.

13. Cabot: *Boston M. & S. J.* **195**:1215 (Dec. 23) 1926.

the left femur, skull, dorsal spine, ribs, scapula, clavicle and bones of the forearm. A pathologic fracture of the neck of the femur was treated by immobilization in a plaster spica, and later it became evident that there was a rapidly growing tumor involving the site of the fracture. Biopsy was performed, and roentgen therapy was administered. The patient lived eight months after admission to the hospital. Autopsy was performed and showed osteitis deformans and osteogenic sarcoma of the left femur with metastasis to the skull and brain.

Von Albertini¹⁴ described in minute detail the development of sarcoma in a case of Paget's disease. His patient was known to have had osteitis deformans of the left femur and tibia for five years. The patient subsequently developed a tumor of the femur for which amputation of the thigh was performed. Examination of the specimen showed that both the femur and the tibia were the seat of Paget's disease and osteogenic sarcoma. The patient survived amputation but two months and exhibited evidence of metastasis to the liver and local recurrence in the stump at the time of his death. Autopsy revealed a thrombotic tumor in the left common iliac vein extending into the inferior vena cava, also metastases to the lungs, epicardium, bronchial and retroperitoneal lymph nodes, kidney and liver. Excellent photomicrographs showed the histologic appearance of the osteitis deformans, presarcomatous changes in certain areas and, in other places, actual sarcoma. Von Albertini remarked that a long-standing osteitis deformans constitutes a presarcomatous condition.

Gold¹⁵ described the case of a man, aged 63, who had broken his arm twenty-three years and ten years previously; there was a tumor destroying from 8 to 10 cm. of the proximal portion of the humerus. Roentgen examination gave evidence of Paget's disease. Histologic examination showed the sarcoma to be of the round cell type.

Our study includes a total of 71 cases of osteogenic sarcoma in patients over 50 years of age. Twenty cases were collected from the records of the Memorial Hospital and 51 were from the Bone Sarcoma Registry. As shown in table 1, the association of osteogenic sarcoma and Paget's disease is relatively the same in the two series. The percentage in the series from the Memorial Hospital was 30 and in that from the Bone Registry it was 27.4, with a percentage of 28 for the total number. Such a frequent association of two apparently dissimilar diseases justifies a careful study of the features presented in the different cases.

14. von Albertini, A.: *Virchows Arch. f. path. Anat.* 268:259, 1928.

15. Gold, H.: *Wien. med. Wchnschr.* 77:1700, 1927.

The cases of all patients over 50 years of age with osteogenic sarcoma were studied. As shown in table 2, the incidence of osteogenic sarcoma decreases in frequency in each half-decade age-group over 50 years. The oldest patient with osteogenic sarcoma whose case was on record in the Bone Registry was 77 years of age, and in this patient the sarcoma was not associated with Paget's disease. In the series from the Memorial Hospital there are no cases of Paget's disease complicated by osteogenic sarcoma in patients under 50 years of age. This in itself is an important feature and it is further emphasized in

TABLE 1.—*Association of Osteogenic Sarcoma and Paget's Disease **

	Memorial Hospital	Bone Sarcoma Registry	Total
Number of patients over 50 years of age with osteogenic sarcoma	20	51	71
Number of patients over 50 years of age with osteogenic sarcoma and Paget's disease.....	6	14	20
Percentage of cases with two diseases associated.....	30	27.4	23.1

* Case E. S. in the series from the Memorial Hospital is also included with the cases from the Bone Registry.

TABLE 2.—*Decrease of Frequency in Incidence of Osteogenic Sarcoma in Patients Over 50 Years of Age **

Ages by Half Decades	Patients with Osteogenic Sarcoma Alone	Patients with Osteogenic Sarcoma and Paget's Disease
50 to 55.....	18	1
55 to 60.....	13	6
60 to 65.....	8	5
65 to 70.....	7	6
70 to 75.....	5	2
75 and over.....	1	0

* There are, however, four cases in the Bone Sarcoma Registry of osteogenic sarcoma associated with Paget's disease in patients under the age of 50. Three of the patients were men and one was a woman. Their ages were 35, 37, 42 and 47.

table 2. In the half-decade age-groups, the highest percentage is found in persons between 65 and 70 years, in which six of the seven, or 85.7 per cent, of the patients with osteogenic sarcoma had Paget's disease. The percentages decrease above and below this peak.

Osteogenic sarcoma appears slightly more common in men than in women (29 men, 22 women). This is substantiated by a series of 121 osteogenic cases studied by the authors in which there were 74 men and 47 women. In the series with Paget's disease and osteogenic sarcoma, men were affected over five times more frequently than were women (17 men, 3 women). This may be due to the fact that the diagnosis of Paget's disease is made more often in men than in women and, to a lesser extent, it may be due to the increased susceptibility of men to osteogenic sarcoma.

The sites of predilection of osteogenic sarcoma in the skeleton in patients over 50 years of age correspond closely to those found at any age except for the increase in frequency of involvement of the flat bones, as shown in table 3. Involvement of the scapula is particularly common, appearing in nine of the fifty-one cases, although Paget's disease was not associated in any of these cases. Approximately 60 per cent of the osteogenic sarcomas of the tibia, humerus and ilium and 100 per cent of the cases of osteogenic sarcoma of the skull occurred on the basis of a preexisting Paget's disease. Therefore, in a patient over 50 years of age, presenting an osteogenic sarcoma of the skull, there is a strong probability of an associated Paget's disease.

In our series, when Paget's disease was present it was demonstrated by roentgen examination in the bone involved by the osteogenic sarcoma,

TABLE 3.—*Location of Primary Tumor*

	Long Bones											Flat Bones		
	Femur	Humerus	Tibia	Ulna	Mandible	Radius	Clavicle	Fibula	Rib	Metacarpal	Vertebra	Scapula	Ilium	Skull
Osteogenic sarcoma in all patients over 50 years of age.....	28	8	6	2	2	1	1	1	1	1	1	9	5	2
Osteogenic sarcoma and Paget's disease in patients of the same group over 50 years of age.....	6	5	4	0	0	0	0	0	0	0	0	0	3	2

and in no instance was the sarcoma found to affect a portion of the skeleton free from roentgenographic evidence of Paget's disease.

The duration of Paget's disease before the appearance of osteogenic sarcoma is difficult to determine either by the history or by the physical examination. The patient may have had Paget's disease many years before attention was attracted to the insidious changes taking place. This is particularly true in women. However, Paget's disease is rarely reported in patients under 30 years of age and seldom in patients under 40 or 45 years. This is important, as osteogenic sarcoma is not found to complicate Paget's disease until the age-group of from 55 to 60 is reached. It seems highly probable that an interval of from ten to fifteen years is present between the final period for the onset of Paget's disease and the appearance of a complicating osteogenic sarcoma. In the histories we find this partially substantiated. Only five of the patients were aware of Paget's disease with its deformities. Two of these gave a positive history of a duration of eight years; one, "many years"; one, ten years, and one, twenty years. One of these

patients was under our observation for ten years with Paget's disease and developed an osteogenic sarcoma at the distal end of the humerus. The question may be raised of the possibility of two or more osteogenic tumors arising on the basis of Paget's disease in one patient. This was demonstrated in two patients in the series from the Memorial Hospital (cases 1 and 11). The assumption that the tumors were primary seems analogous to that of multiple independent squamous cancers arising on leukoplakia. Ordinarily, osteogenic sarcoma infrequently metastasizes to bone.

DURATION OF LIFE

The duration of life from the onset of the osteogenic sarcoma to death in patients with and without Paget's disease is relatively the same in the group from the Memorial Hospital, as shown in table 4. In considering the total number of cases, one finds that patients with

TABLE 4.—*Duration of Life*

	Patients with Osteogenic Sarcoma		Patients with Osteogenic Sarcoma and Paget's Disease	
	Number	Average Number of Months	Number	Average Number of Months
Memorial Hospital.....	10	18.7	4	16.0
Bone Registry.....	23	26.3	11	14.4
Total.....	33	24.0	15	14.8

osteogenic sarcoma and Paget's disease die approximately ten months earlier than patients with osteogenic sarcoma alone.

DIFFERENTIAL DIAGNOSIS

Paget's disease with an associated sarcoma must be distinguished from: (1) metastatic tumors of the bone (osteogenic sarcoma; the myelomas); (2) metastatic carcinoma of undetermined origin, especially prostatic carcinoma; (3) Paget's disease combined with syphilis of the bone or chronic infection, and (4) atypical cases of osteitis fibrosa cystica, multiple form, with the formation of giant cell tumors.

HISTOLOGY

The histologic picture of Paget's sarcoma differs from that seen in uncomplicated osteogenic sarcoma. It is of interest to quote from the opinions of several of the pathologists on case 772 of the Registry, which is case 11 of the series from the Memorial Hospital.

. . . one of the vagaries that occurs among the malignant tumors developing in Paget's disease. It seems to me that these cases should have a separate

division in the Registry classification, for they represent a different clinical entity from the usual osteogenic sarcoma. Some day this group may be particularly important in giving a clue to the origin of sarcoma.

Another writes:

This is not a typical osteogenic sarcoma. It belongs essentially among the variants of giant-cell tumors. It shows a great many giant cells, but many of these are mononuclear and hyperchromatic. The main cell is large and polyhedral. There is much lymphocytic infiltration. In men over 50 years of age and especially in patients with osteitis fibrosa, giant cells tend to recur locally and become malignant.

Five others simply report osteogenic sarcoma in Paget's disease.

The presence of giant cells in this tumor should not lead to the belief that the condition is benign. These giant cells differ from those found in epulis tumors. They are usually hyperchromatic and not necessarily multinuclear. Their exact relation to Paget's disease is not well understood.

PROGNOSIS

The 100 per cent mortality rate of patients with the two diseases may be explained on several grounds. In the first place, patients who are accustomed to the "growing pains" associated with Paget's disease are not apt to seek medical advice as soon for a change in the character of the pain as patients with osteogenic sarcoma unassociated with Paget's disease; in the second place, the pathologic changes due to Paget's disease may delay the onset of the pain from an osteogenic sarcoma, and last, osteogenic sarcoma arising in Paget's disease may have more malignant qualities than this primary tumor of the bone in normal patients past middle life.

In the group from the Memorial Hospital, irradiation was done in four of the six cases in which the two diseases occurred; amputation was done in two cases, and in one case the disease was too far advanced for any treatment. Amputation was performed in twelve of the fourteen cases from the Bone Registry. We have been unable to find any record of a case of osteogenic sarcoma associated with Paget's disease in which the patient has survived a period of five years.

TREATMENT

It would appear that some change from the ordinarily accepted methods of treatment is worthy of trial. In one of our cases (case 3), the patient was subjected to heavy external radiation by radium pack and exposure to high voltage x-rays, and amputation was performed about six months later. He received injections of the mixed toxins

of erysipelas and *Bacillus prodigiosus* following operation. These injections were given intravenously and were accompanied by severe reactions.

It may be that the use of preliminary radiation and of treatment with toxin following amputation will prove less disappointing than amputation alone.

REPORT OF CASES

CASE 1.—*Osteogenic Sarcoma Complicating Paget's Disease.*

History.—A man, aged 63, was admitted to Memorial Hospital on Aug. 26, 1928. The condition had begun nine months prior to admission with initial symptoms of stiffness and pain in the left knee. Five months later, he noticed a swelling in this location. He was treated with baking and massage under the assumption that the condition was rheumatism, but no relief was obtained, the pain growing steadily worse and the swelling becoming progressively larger. Early in July he was admitted to the Hospital for Joint Diseases, where a diagnosis of Paget's disease was made. There was no pain or swelling in any other part of the body; there was little loss of weight. There was no history of specific antecedent trauma. His immediate family history was negative for malignant diseases. He had been able to work steadily for about four months prior to his admission to Memorial Hospital.

Physical Examination.—The patient was a wiry male, aged 63, well developed and nourished, although showing slight loss of weight. Examination of the head revealed several bony enlargements and irregularities of the skull. These were discrete on palpation, but not painful. There were several other smaller and more questionable areas. The pupils were equal and reacted to light and accommodation. The teeth were replaced by dentures. The gums were smooth and there were no ulcerations. The mucous membrane was normal. The tonsils were enlarged, protruding into the pharynx; there was no apparent involvement. The tongue was normal. There were no enlarged glands in the neck. On inspection of the trunk, there was obvious distortion of the clavicles, more pronounced on the left side. The heart and lungs were essentially normal, except for some dulness in the base of the right lung with increased breath sounds and a slight systolic murmur transmitted toward the left axilla. The abdomen showed inguinal hernia on the right side. The rest of the examination gave negative results. The examination of the extremities was of special interest. The left upper extremity was apparently normal. The right elbow and lower part of the humerus showed a distinct enlargement, which was diffuse and not sharply outlined above. There was an enormous tumor of the lower part of the left thigh which entirely obliterated the anatomic markings of the knee. It occupied the anterior and middle aspects of the lower part of the thigh and extended less than half way up the thigh. The skin was shiny and discolored in areas, being dark bluish red and blotchy in appearance. There was some dilatation of the superficial veins of the skin. The lower part of the leg was diffusely swollen, owing to lymphatic and venous obstruction, and presented an appearance similar to elephantiasis. The lower part of the right leg showed a profound alteration of the normal subcutaneous outline of the tibia. There was the characteristic bowing seen in Paget's disease. On September 6, measurements showed that the circumference of the left limb at the patella was $25\frac{1}{4}$ inches (64.095 cm.) and that of the right limb $15\frac{1}{4}$ inches (38.175 cm.).

Roentgen examination of the femora, pelvis, spine, skull and chest revealed the characteristic features of Paget's disease. A roentgenogram of the left knee revealed extensive destruction of the inner tuberosity of the humerus with calcareous deposits in a huge soft mass. The Wassermann examination was negative.

Clinical Diagnosis.—A clinical diagnosis of Paget's disease with osteogenic sarcoma of the left femur and questionable metastasis of the right humerus was made. This was supported by the results of the roentgen examination. The disease was so far advanced that amputation was felt to be out of the question.



Fig. 1.—Sarcoma of the left femur. Paget's disease is evident in the right tibia.

Moreover, the tumor was so huge that toxemia from absorption of broken-down tumor tissue was about all that could be reasonably expected to result from treatment with x-rays or with radium. Therefore, no treatment of any kind was advised.

Laboratory Examination.—The Wassermann test of the blood was negative. The urine showed traces of albumin and casts. The blood count on admission was: hemoglobin, 55 per cent; red blood cells, 2,720,000; white blood cells, 10,000; polymorphonuclears, 81 per cent. No abnormal cells were noted.

On August 30, there was 10.3 mg. of calcium per hundred cubic centimeters in the blood.

Comment.—The histologic report in this case is of interest, showing as it does stages coexistent in the bone marrow ranging by gradual gradations from simple chronic inflammatory changes into definite osteogenic sarcoma. The fact that five months elapsed in this case between the initial pain and the development of a swelling emphasizes the importance of early roentgenologic examination in persons with persistent pain in the bone. It is worthy of note that a diagnosis of Paget's disease was not made until the patient already had an osteogenic

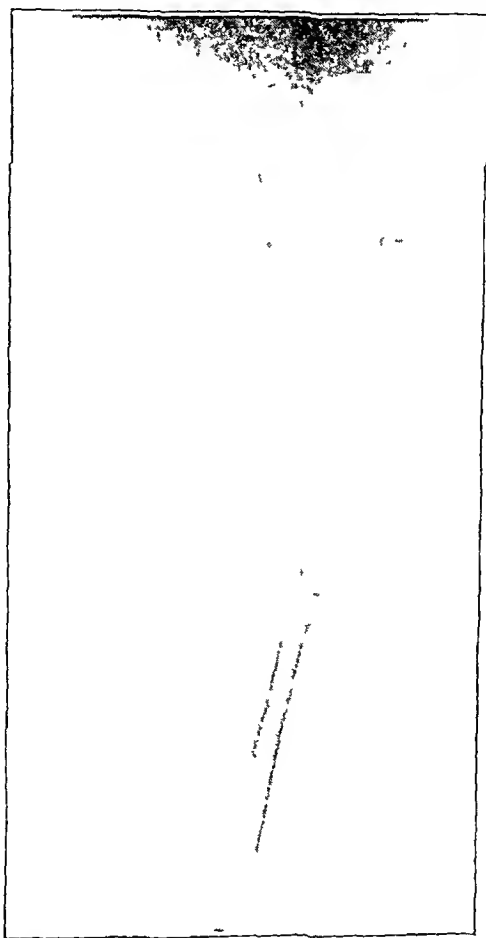


Fig. 2.—Roentgenogram showing sarcoma of the left femur.

sarcoma. It would seem to be important to caution the members of the medical profession concerning the need for careful observation in all persons with Paget's disease because of the potential danger of subsequent development of an osteogenic sarcoma.

CASE 2.—Osteogenic Sarcoma of the Lower Part of the Right Tibia Complicating Paget's Disease.

History.—A man, aged 68, was admitted to Memorial Hospital on June 23, 1927. In February, 1924, he had sustained an injury to his back and legs in an

automobile accident and remained in bed for ten weeks. During that time he noticed swelling, pain and discoloration of the upper third of the right tibia. In March, 1925, one year after the accident, a biopsy was done and the pathologic report showed a malignant tumor of the bone on the basis of a preexisting Paget's disease. Amputation was performed shortly thereafter. About two years elapsed without symptoms and in May, 1927, he was referred to us with symptoms of severe pain in the right forearm and total disability of the arm.

Physical Examination.—Examination showed a man in rather poor general condition. Examination of his lungs disclosed crepitant râles over both sides of



Fig. 3—Gross appearance of the tumor (autopsy).

the chest posteriorly, especially at the base. This condition did not disappear on coughing. There were many small pigmented areas of skin on the back. The right leg had been amputated at the junction of the middle and upper thirds with no local recurrence. There was swelling of the right forearm more marked on the ulnar aspect.

Roentgen examination on July 20 showed extensive destruction of the upper half of the right humerus and the upper half of the ulna.

On June 11, a roentgenographic report had showed no evidence of metastasis to the chest.

Treatment.—The patient was given radium element pack for 25,000 millicurie hours at a distance of 10 cm. over the right forearm posteriorly, and one exposure

of high voltage x-rays. The upper half of the right humerus also received one treatment with high voltage x-rays. Thirteen injections of the mixed toxins were also given. The treatments were not followed by any demonstrable improvement and the patient was discharged on July 28, after a five weeks' stay in the hospital. He died one month later.

CASE 3.—*Osteogenic Sarcoma of the Left Humerus Complicating Paget's Disease.*

History.—A man, aged 57, about two months prior to admission began to have pain in the left shoulder, which he attributed to a sprain in the course of his occu-



FIG. 4.—Roentgenogram of the tibia of a patient with Paget's disease and osteogenic sarcoma, with the later development of a second osteogenic sarcoma of the ulna.

pation as a chauffeur of a passenger bus. He rubbed the painful area with liniment and later consulted a doctor for another condition, casually mentioning the pain in his shoulder. Roentgen examination was then made, and a diagnosis of probable sarcoma of the humerus was rendered. No mention was made at this time of Paget's disease. There had been a loss in weight of from 15 to 20 pounds (6.8 to 9 Kg) in the last year. The patient had never had any serious illnesses. He had lost no time from his work on account of illness in the past thirty years. For many years, however, he had had cramplike pains in the legs at night (suggestive of Paget's disease).

Physical Examination.—The patient was a well developed, poorly nourished man, about 60 years old, with marked tortuosity of the temporal arteries. The skull showed a number of irregular bosses, and an increase in the transverse diameter. The nose was normal. The teeth were completely replaced by dentures. The tongue was clean. The neck showed no palpable masses, scars or abnormal pulsations. The chest was symmetrical and expansion was equal. The costal angle was acute and there was a slight Harrison's groove. The lungs were resonant throughout. The abdomen was normal. There was a marked anterior bow-

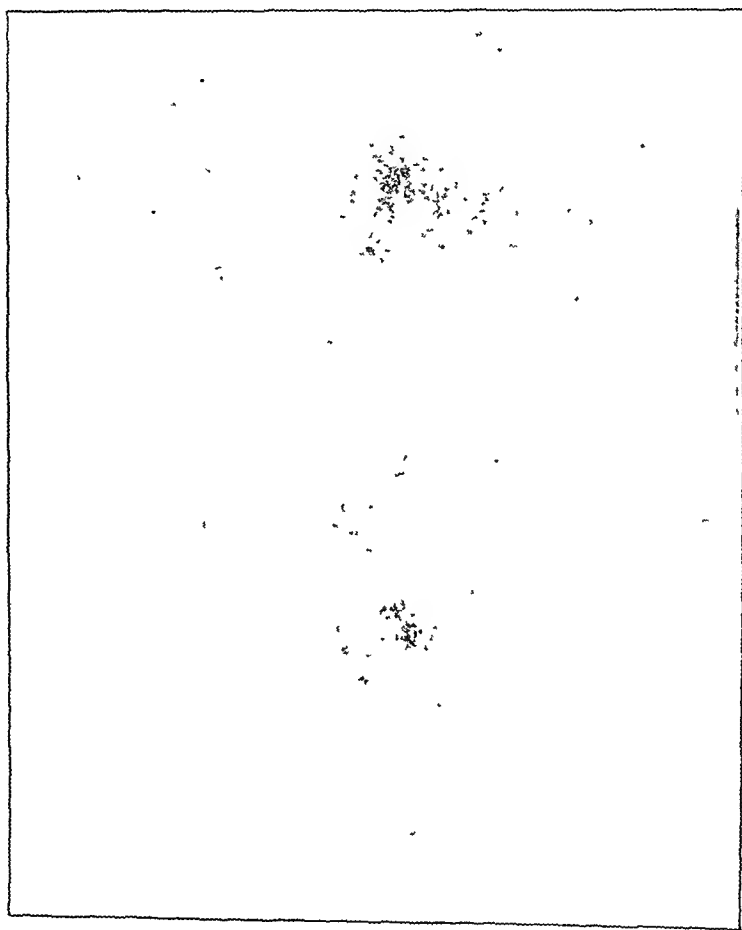


Fig. 5.—Paget's disease of the skull.

ing of the right femur and tibia which was obvious both on inspection and palpation.

Roentgenograms were made and the following report was rendered by Dr. Herendeen on July 26, 1929:

"Roentgenograms of the skull, left femur, pelvis and tibia reveal the characteristic features of Paget's disease. Stereoscopic views of the left shoulder reveal the presence of the same process in the clavicle, scapula and humerus. In addition, a large area of destruction of the bone is noted in the outer, upper third of the shaft of the humerus."

A second report, on September 11, was as follows: "A film of the lungs does not show definite evidence of metastases."

Treatment.—Treatment was commenced on August 9 and in four days the patient received four treatments with radium element pack for a total of 16,000 millicurie hours at a distance of 6 cm. On August 7, August 10 and September 12, he received three treatments with high voltage x-rays, each exposure lasting twelve minutes and consisting of 175 kilovolts given at a distance of 50 cm. from



Fig. 6.—Paget's disease of the tibia.

the skin, at a milliamperage of 30 through a port 10 by 10 cm. in size, the filtration being 0.5 mm. of copper, and all treatments being given to the left shoulder.

During these treatments and thereafter his arm was immobilized in a sling and a swathe. He returned to the outpatient department of the Bone Clinic for frequent observation. The pain became progressively more severe, and the tumor grew. That this represented continued growth of the sarcoma should not be assumed, as the effect of radiation on an osteogenic sarcoma is often to produce

swelling. However, the patient was unable to tolerate the pain and finally consented to amputation. It was necessary to perform an interscapulothoracic disarticulation because of the extent of the growth. This was done on Feb. 6, 1930. The patient made a smooth recovery following the initial shock which was forestalled in large measure by a transfusion given on the table at the end of the operation. Twelve days postoperatively, the injections of toxin were commenced, and ten were given. The wound healed promptly without infection. The patient was discharged on March 7, and has been observed regularly in the clinic. He

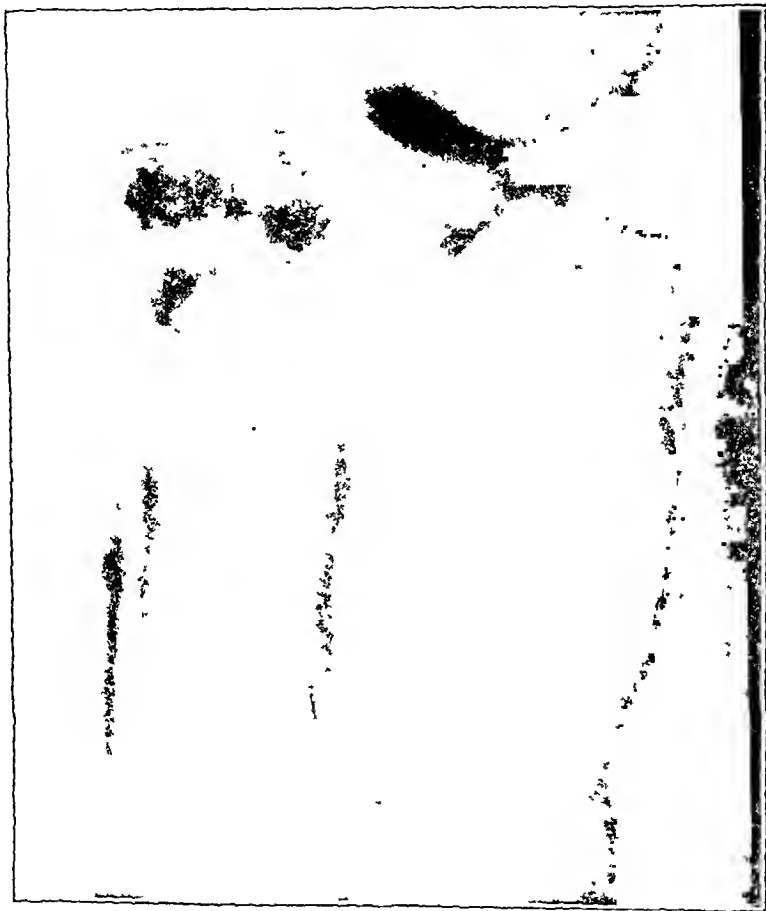


Fig 7.—Paget's disease of the humerus with osteogenic sarcoma.

was last seen on November 13, nine months after amputation. At that time he was free from symptoms and showed no evidence of disease and a roentgenogram of the chest showed no evidence of metastases.

CONCLUSIONS

1. From a study of cases of osteogenic sarcoma in Memorial Hospital, it was found that in no patient was this condition associated with Paget's disease prior to the age of 50.
2. In a collected series from Memorial Hospital and the Bone Registry of seventy-one cases of osteogenic sarcoma in patients over

50 years of age, Paget's disease was found to be a predisposing factor to osteogenic sarcoma in 28 per cent.

3. Of patients with the two diseases associated, men are affected five times more frequently than women.

4. In general, it may be said that osteogenic sarcoma in patients over 50 has the same sites of predilection as in younger persons.

5. A patient over 50 with osteogenic sarcoma of the skull presumably has Paget's disease.

6. When osteogenic sarcoma is associated with Paget's disease, it invariably develops in a bone showing the characteristic changes of Paget's disease rather than in an otherwise normal bone.

7. Evidence is presented to show that Paget's disease is present from ten to fifteen years or more prior to the development of a complicating osteogenic sarcoma.

8. The duration of life is shortened by the association of osteogenic sarcoma with Paget's disease, as determined by a comparative study of a group of patients of the same age without osteogenic sarcoma.

9. No record has been found of the survival for five years of a patient with osteogenic sarcoma and Paget's disease under any method of treatment.

10. Paget's sarcoma has proved to be relatively resistant to radiation.

11. Preliminary radiation by intensive exposure to radium pack and high voltage x-rays and, following amputation, the use of prophylactic constitutional therapy with the mixed toxins are suggested as a method worthy of trial.

THE MECHANISM OF THROMBOPHLEBITIC EDEMA *

LEO M. ZIMMERMANN, M.D.

AND

GÉZA DE TAKÁTS, M.D.

CHICAGO

PREVIOUS LITERATURE

The mechanism of the edema that follows thrombophlebitis of the extremities has provoked considerable discussion for many years. Repeated experimental investigations have tended to support first the theory of venous obstruction, then that of lymphatic origin, without having served to bring the problem to definite decision. Many years ago, Cohnheim¹ showed that ligation or extirpation of all of the lymphatics from an extremity fails to produce edema of that limb. These experiments have been repeated many times since then, with numerous variations, and usually with the same results. Clinical observations, however, of edemas following mechanical extirpations of lymph nodes or the compression of the lymphatics by tumor growth have given constant support to the belief that lymphatic obstruction will sufficiently interfere with the return of fluid to result in edema of the extremity. The clinical improvement noted after surgical procedures intended to provide new lymphatic pathways from edematous limbs, such as Handley's lymphangioplasties,² and the Lanz³ and Kondoleon⁴ operations, which are directed toward providing anastomoses between the

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* From the Department of Surgery and the Laboratory of Surgical Research, Northwestern University Medical School.

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superficial and deep sets of lymphatics, has given further support to the lymphatic theory.

Attempts to produce edema experimentally by ligation of the veins go back to the researches of Lower, in 1680.⁵ He succeeded in producing edema in various parts of the body by tying the veins, but subsequent workers have failed to repeat his results. Ranvier⁵ found that ligation of the femoral veins would not produce edema, but simultaneous ligation of the veins and division of the sciatic nerve produced this result. In 1879, Sotnitschewsky,⁶ working in Cohnheim's laboratory, failed to produce edema by either of the methods mentioned, and found that by making the injections into the veins after ligation, fluid easily passed through collateral vessels. He found, however, that the injection of plaster of paris into the veins of the foot, with the application of a constrictor about the thigh until the plaster had set, produced massive edema of the extremity.

At the present time there is a growing tendency to ascribe the edemas of the extremities following thrombophlebitis to obstruction of the lymphatics.⁷ Homans felt that the phenomena consequent on thrombophlebitis of the iliac vessels are incompatible with mere venous obstruction, and he recently reported experimental work that tends to show that the main lymphatic channels of the extremities, which run in close proximity to the iliac veins, are involved in the periphlebitic inflammation, and that it is the obstruction of these channels that is responsible for the postphlebitic edema.⁸ In his experiments Homans found, as have many others, that simple ligation of the femoral or the iliac vein or both does not result in edema of the leg of the dog. The injection of bacterial emulsions, however, into an isolated segment of the external iliac vein produced an infectious thrombus and marked edema of the entire extremity. From his studies, Homans concluded that the cause of phlegmasia alba dolens is a lymphatic obstruction due to the inflammatory reaction around an area of thrombophlebitis, and that the basic lesion is always in the common or external iliac vein, however far it may extend peripherally.

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6. Sotnitschewsky: *Ueber Stauungsödem*, *Virchows Arch. f. path. Anat.* **77**:85, 1879.

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METHODS OF EXPERIMENTATION AND RESULTS

We set out to repeat the experiments of Homans. The experiments were performed on the hind legs of dogs, the opposite limb in each animal being used for control. All operative procedures were carried out under ether anesthesia, with morphine premedication, and the usual aseptic precautions were observed. The experiments fall into a series of groups that led to the development of a simple, reliable method of producing edema comparable to that which follows human thrombophlebitis. Analysis was then made of the possible factors involved, so that the mechanism of the formation of edema and some of its characteristics could be determined.

Simple Ligation of the Iliac and Femoral Veins.—In the first group of animals the following veins were ligated: the common iliac vein on one side, the common and the internal iliac veins of the same side, both common iliac veins, both common plus both internal iliac veins, the femoral vein and the femoral plus the iliac veins of the same side. None of these measures produced noticeable edema of the leg. In many of the subsequent experiments, ligations of the veins of one or both sides were done in addition to other procedures, also without resulting in the development of edema. These results are in accord with those of Homans and others in laboratory animals, and are comparable to those reported in man when the surgical ligation of the main veins of the extremity have not resulted in edema or any other circulatory disturbance.

Chemical Phlebitis and Periphlebitis of the Iliac Veins.—In another group of animals we sought to repeat the experiments of Homans. Instead of using emulsions of living bacteria, however, which might conceivably spread beyond the regions intended, we used chemical irritants similar to those in use in the obliteration of varicose veins. Fifty per cent solution of sodium salicylate, in amounts varying from 2 to 6 cc., and tincture of iodine, from 2 to 8 cc., were injected into isolated segments of the common and external iliac veins. In some experiments some of the solution was sprinkled along the outside of the vein. In all of the animals there was considerable periphlebitic reaction, even to necrosis of the perivenous tissues, with or without thrombosis in the isolated segment. In none of these animals was there edema of the leg.

Mechanical Extirpation of the Iliac Lymph Glands and Lymph-Bearing Tissues.—Having failed to produce edema of the leg by causing periphlebitic inflammation with presumable involvement of the adjacent principal lymph channels, we attempted to interrupt the lymphatic return

from the extremity by mechanically dissecting out the iliac lymph glands together with all of the retroperitoneal fatty and areolar tissues from the bifurcation of the aorta to Poupart's ligament, and from the posterior parietal peritoneum to the psoas muscles. The common and internal iliac veins were ligated and divided at the same time, only the artery being left intact. In some experiments even the adventitia of the artery was dissected off, to exclude any contained lymphatics. In the first animal operated on, marked edema of the entire thigh and leg developed. Dry gangrene of the leg subsequently ensued, because of a traumatic thrombosis of the artery and of the vein. Two other animals had slight, transient edema, in one of which extensive thrombosis of the veins extending down into the leg was found. In the remaining eight animals of this group, there were no traces of edema, although in several the dissection was repeated to remove any regenerated lymphatics and the collateral veins were ligated. The failure to produce edema in these experiments seemed to indicate that interruption of the lymph channels along the iliac vessels was not sufficient to produce edema of the corresponding limb; and while we could not be sure that all lymph vessels were removed by our operation, there was much more inflammation of the adjacent tissues as a consequence of the dissection than could be expected to result from an inflammatory process within the iliac veins.

Peripheral Injection of Irritants into Veins.—Our next attempt was to produce an extensive peripheral venous obstruction, by the injection of irritants peripherally, from the femoral veins. The vein into which the injection was to be made was exposed through a short incision just below Poupart's ligament and freed from its surrounding structures, and a ligature was placed just below the ligament. A needle was then tied into the vein, pointing downward and the injections made. Fifty and 70 per cent alcohol was used, in amounts of from 10 to 20 cc. In practically every one of these animals, marked edema ensued (fig. 1). The swelling developed during the first twenty-four hours, reached its maximum in from two to three days, then gradually subsided, and disappeared entirely in from two and one-half to three and one-half weeks. The edema appeared first and was most marked in the thigh, extending later to involve the entire leg and foot. In some of the animals it advanced also to the anterior abdominal wall, sometimes reaching as high as the xiphoid process. When most severe, the swelling was firm and brawny; when less marked, it was soft and pitting. At autopsy, extensive thrombosis or fibrous obliteration of the femoral veins was found, with marked perivenous infiltration. In some instances, there was actual necrosis and abscess formation.

These experiments indicated that the peripheral injections of chemical irritants into the main veins of the extremity resulted in edema of the limb, and suggested that the swelling was due to extensive peripheral block of the venous return. Two factors, however, still had not been ruled out, the perivenous inflammation that might affect the concomitant lymph channels and a possible direct effect of the irritant on the wall of the vessel, leading to increased permeability and exudation.

Production of Intravascular Thrombosis.—To avoid the criticisms indicated in the preceding paragraph, we sought for a bland, obturating agent that would occlude the vessels and not injure the wall of the vessel or the perivascular tissues. An emulsion of barium sulphate in



Fig. 1 (dog 35).—Edema of the leg twenty-four hours after the injection of 20 cc. of 50 per cent alcohol into the left femoral vein.

gelatin was injected into a series of five dogs. Edema of an extreme degree resulted in all of the animals. Three of the five died, and one seemed to have a great deal of pain on awakening, so the procedure was abandoned. Besides, the introduction of a metallic poison, to produce a bland intravascular thrombus, could be severely criticized.

Tissue extracts were then used for the peripheral injection, with the idea of producing bland noninflammatory thrombotic obstruction of the veins. The extracts were made of muscles of the hearts of dogs. Animals on which autopsies had been performed were used. The hearts were removed under aseptic care, minced and extracted with sterile distilled water or physiologic solution of sodium chloride. Injection of such extracts, in amounts from 15 to 30 cc., usually resulted in edema

of the leg, similar to that produced in the earlier experiments (fig. 2*A*). The edema was less uniform in degree than by the other methods, and was missed in a few experiments.

To pursue the idea a step further so as to produce edema by the injection of perfectly bland substances that would cause thrombosis but no perivascular inflammation, a series of animals was given injections of their own serum. Blood was drawn from the heart and allowed to clot, and the serum was reinjected, against the stream, into the femoral veins. In these animals also striking edema of the extremity developed (fig. 2*B*). Here, however, the edema was inconstant and of unequal intensity. The experiments to this point had convinced us that the



Fig. 2.—*A*, edema of the leg three days after the injection of 20 cc. of fresh heart muscle extract into the left femoral vein (dog 36). *B*, edema of the leg two days after the injection of 20 cc. of autogenous serum into the left femoral vein (dog 37).

obstruction of the veins of an extremity, with the use of the blandest possible substances, was followed by the development of edema in that limb. It was difficult to attribute any important rôle to the lymphatics in the mechanism of this edema.

Because of the inconvenience of preparing the extracts of muscles of the heart or the serum for further studies as to the nature and mechanism of the edema, the concentrated tissue extract prepared by C. A. Mills, and sold under the trade name fibrogen (Merrill), was used. Quantities of this preparation as small as from 0.5 to 1 cc. injected peripherally into the femoral vein resulted in extensive thrombosis of the veins and marked edema of the extremity (fig 3).

These edemas, like those following the injection of irritants, developed during the first twenty-four hours, and never lasted for more than from three and one-half to four and one-half weeks (table 1).

Postmortem Observations.—Animals were killed at various intervals after the injections, and the limbs were dissected. In general, the more extensive the edema, the more hemorrhagic the exudate proved to be. In limbs with marked swelling, the tissues were completely infiltrated with a hemorrhagic fluid. In the slight edemas, the fluid was thin and colorless. With the severe edemas there was also a heavy deposit of fibrin on the muscle bundles. The veins were thrombosed in all of

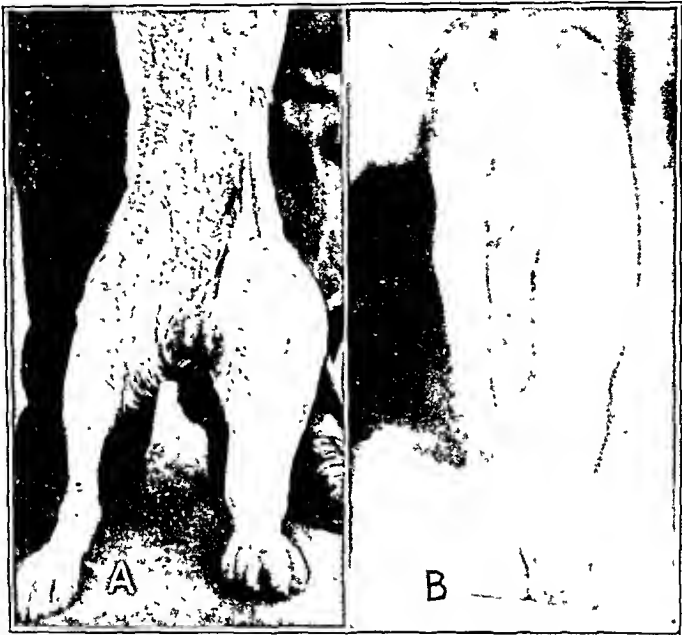


Fig. 3.—*A*, edema following the injection of 2 cc. of fibrogen into the left femoral vein. *B*, edema following the injection of 1 cc. of fibrogen into the right femoral vein.

TABLE 1.—*Circumference of Edematous Limbs (Twenty Hours After Injection of 1 cc. of Fibrogen into the Left Femoral Vein)*

	Dog 91		Dog 92	
	Right	Left	Right	Left
Foot.....	7.0 cm.	8.0 cm.	7.8 cm.	8.5 cm.
Leg.....	10.5 cm.	13.5 cm.	8.5 cm.	13.0 cm.
Thigh.....	23.0 cm.	28.0 cm.	18.5 cm.	26.5 cm.

the animals with edema (fig. 4). the extensiveness of the thrombosis usually corresponding to the severity of the edema. In the milder forms, the thrombosis reached only to the knee; in the severe ones, it extended

to the ankle. The tributaries of the veins were also occluded for a variable distance. The vein seemed to be somewhat more adherent to its surrounding structures in the occluded portions than elsewhere. In a few of the animals, the edema extended to the abdominal wall as high as the xiphoid process. Pulmonary embolism was seen occasionally (figs. 5, 6, 7 and 8).

Protein Content of the Edema Fluid.—It was thought that determinations of the protein content of the fluid might shed some light on the mechanism of the edema. Through the courtesy of Professor Farmer, of the department of chemistry, determinations of the protein content in a series of experiments have been made by the refractometric method (table 2). These determinations indicate a high protein content, the values ranging from 1.25 to 3.4 per cent. It is our impression, however, that the protein content is directly proportional to the severity and

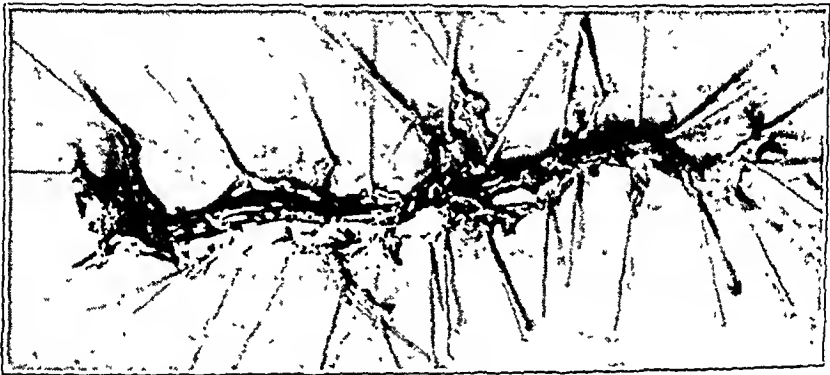


Fig. 4.—Vein dissected out and opened, showing intravascular clot.

TABLE 2.—*Protein Content of Edema Fluid**

Dog	Duration of Edema	Protein Content, per Cent
48.....	24 hours	2.33
57.....	3 days	3.08
62.....	4 days	3.34
63.....	2 days	2.40
50.....	3 days	1.21
80.....	20 hours	2.64
90.....	20 hours	3.30
95.....	20 hours	2.24
96.....	20 hours	3.50

* The determinations were made with the refractometer by Miss Alice Reed, A.B., of the Department of Chemistry.

the duration of the edema. Further studies are now in progress concerning these changes in the chemical nature of the edema fluids.

Injections into the Saphenous Vein.—In a series of four animals, fibrogen was injected into the saphenous veins, in a retrograde direction, from a point close to their junctions with the femoral trunks. In two of

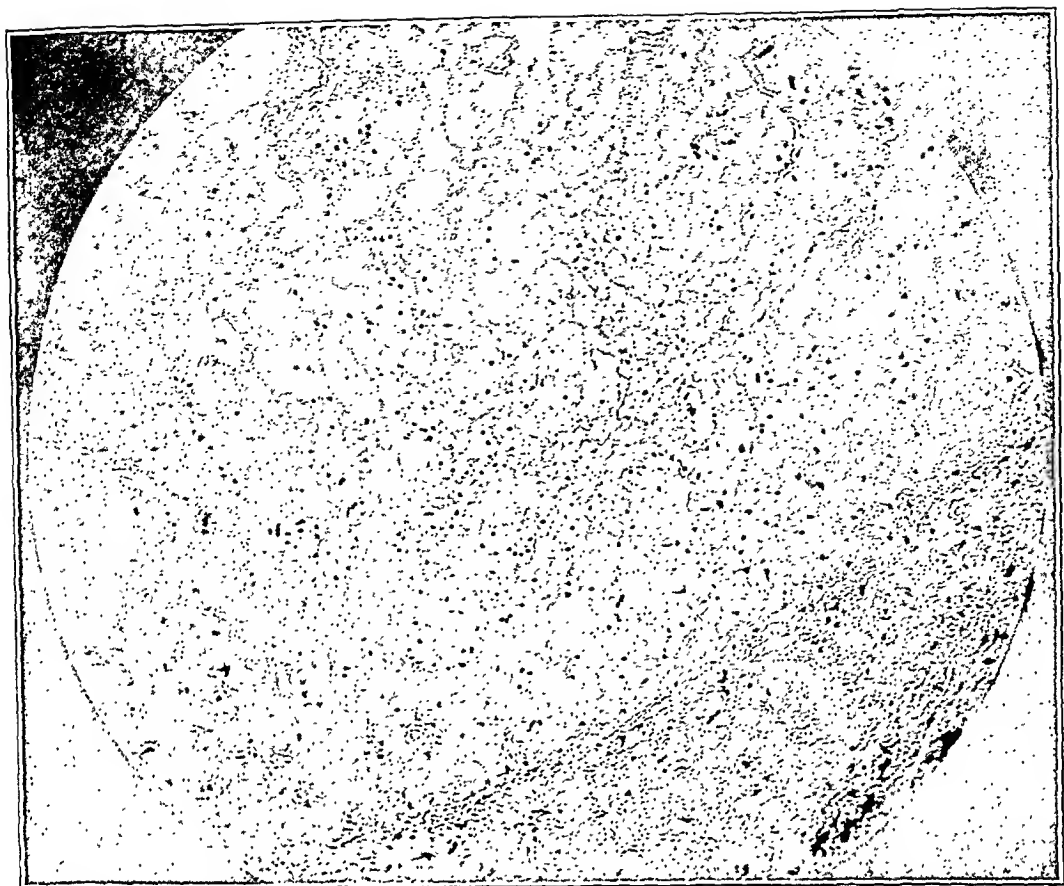


Fig. 5.—Photomicrograph of edematous tissue, showing fibrin strands and slight cellular infiltration.

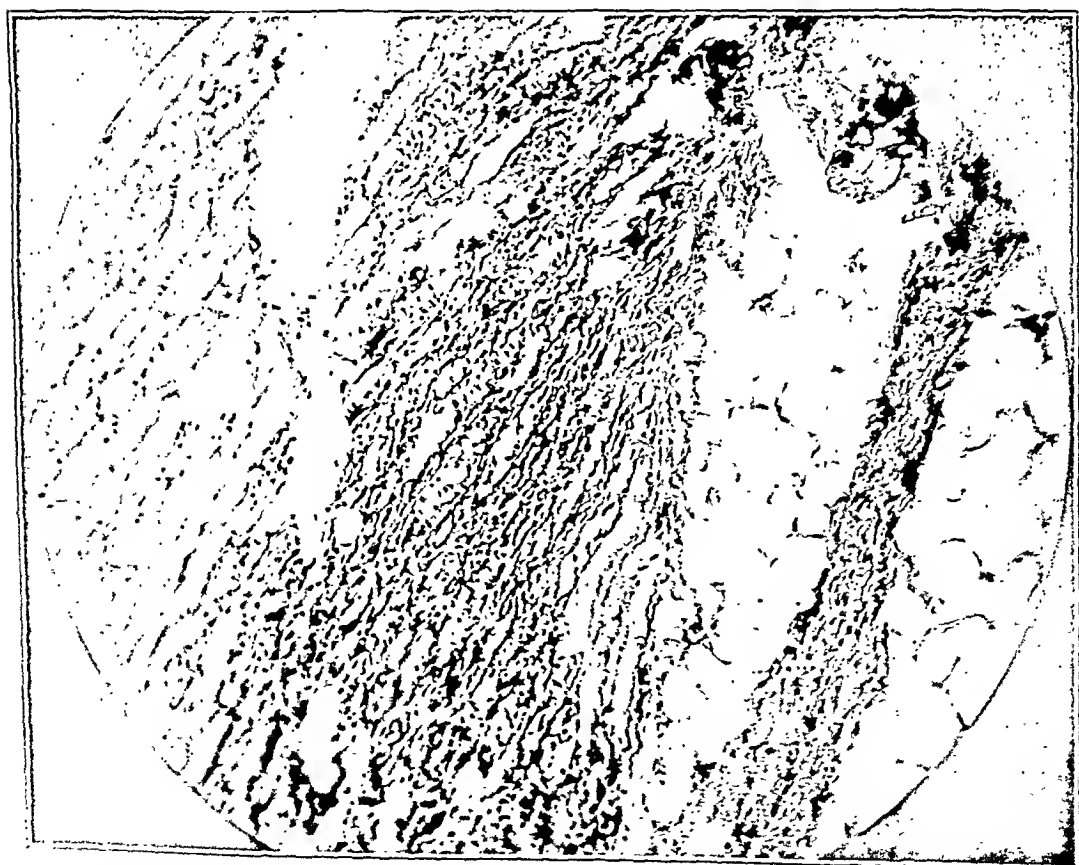


Fig. 6.—Edematous tissue one week after injection, showing organization of exudate.

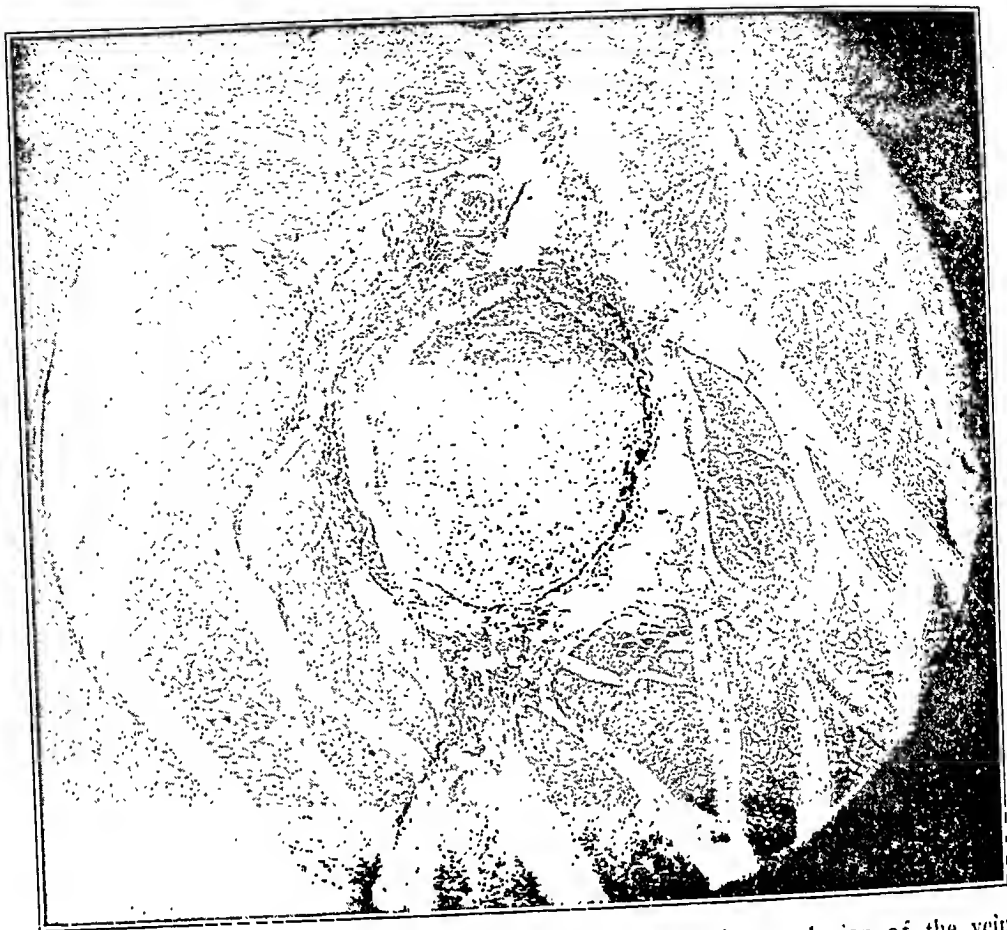


Fig. 7.—Low power section through the leg, showing occlusion of the vein and edema of the tissues. Note the absence of inflammatory reaction about the vein.

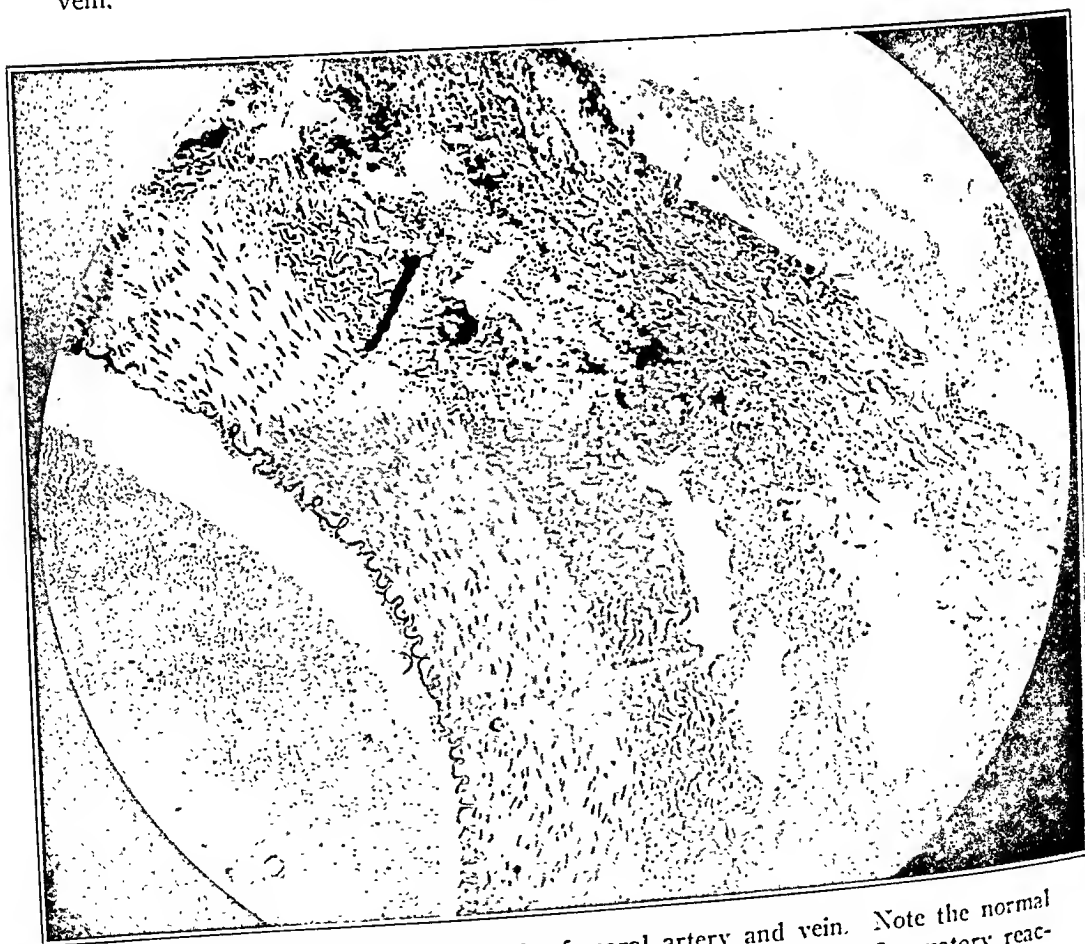


Fig. 8.—Adjacent portions of the femoral artery and vein. Note the normal structure of the artery and the absence of marked perivenous inflammatory reaction.

these experiments, the deep veins were intact. Following the injection, no edema or other circulatory disturbance resulted. In the other two animals, the femoral veins had previously been obliterated by the injection of coagulants. In both of these limbs there was an enormous edema following the obliteration of the saphenous veins. The significance of these few observations for the injection treatment of veins with occluded deep circulation is obvious.

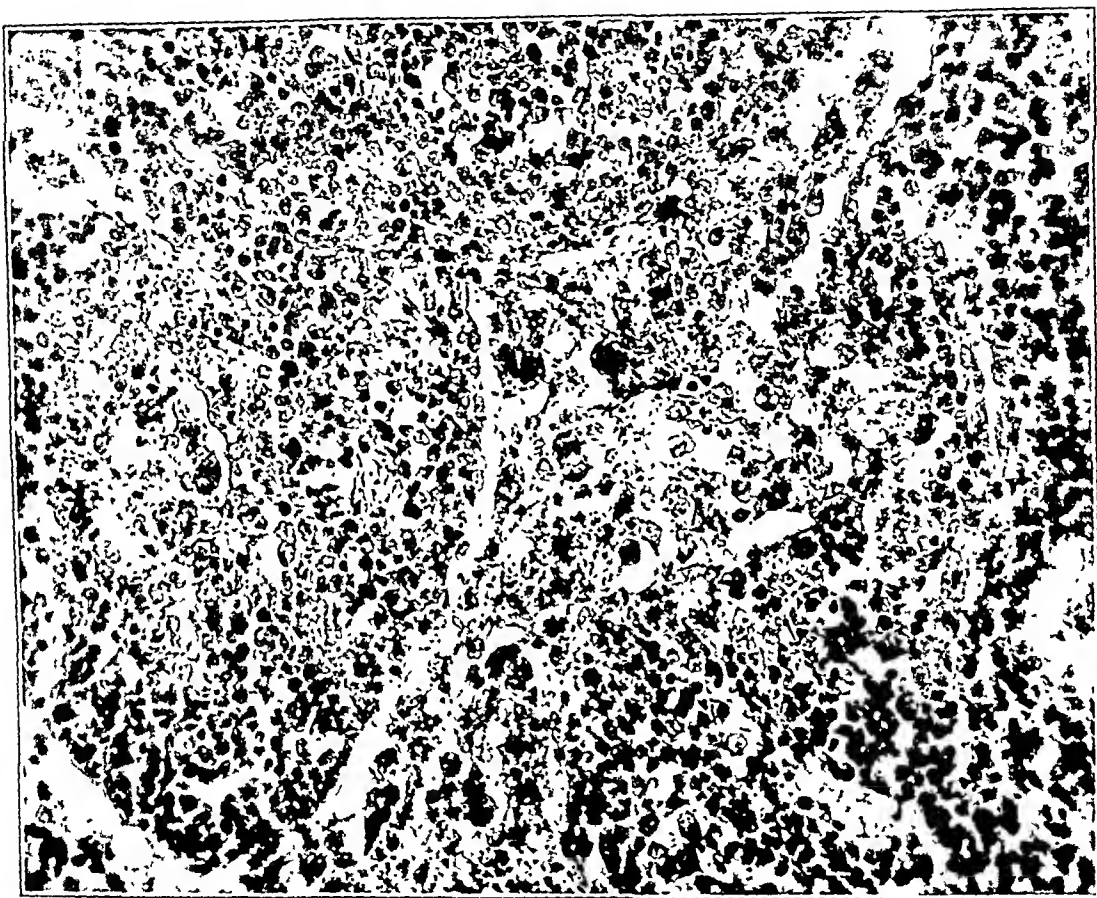


Fig. 9.—Iliac lymph node from an animal into whose foot india ink was injected at the height of edema. Note the fine black particles of ink within the cells, as well as in the lymph spaces.

Experiments with Heparin.—The question rose as to whether the injected substances themselves might not be sufficient to produce the edema, the venous thrombus being but an incidental factor. To rule out this factor, injections were made in the usual fashion, the fibrogen being diluted in a few cubic centimeters of sterile water. The same quantity of fibrogen, diluted with from 200 to 300 mg. of heparin and dissolved in a similar quantity of sterile water, was injected into control animals. In the experiments in which heparin was not used marked

edema resulted, and the veins were found to be extensively thrombosed. In those in which heparin was used, the thrombus was limited to the first 1 or 2 cm. of the vein, and there was no edema.

Injection into the Lymphatics.—In two animals with edema, 1 cc. of emulsion of india ink was injected into the footpads, and the animals were killed after two and one-half and sixteen hours. In the iliac lymph glands of neither of these animals could particles of ink be demonstrated. In control animals into which the same quantity of ink was injected at the same time and which were killed after the same intervals, pigmentation of the iliac glands was observed. India ink was injected into two other animals with marked edema of the legs, and the animals were killed after twenty-four hours. In both, ink was recovered in the iliac glands (fig. 9). In another series of four animals, the injections

TABLE 3.—*Summary of Experiments*

Type of Experiment	Number	Edema in
Ligation of veins alone.....	7	0
Ligation plus injection of irritants into iliac veins.....	6	0
Mechanical extirpation of lymphatics.....	12	3
Alcohol injected peripherally (femoral).....	17	17
Injections of barium-gelatin emulsion	5	5
Injections of heart muscle extract.....	17	16
Injections of autogenous serum	10	8
Injections of fibrinogen	41	41
Heparin injected (plus fibrinogen or muscle extract).....	6	2
Fibrinogen injected into saphenous vein.....	4	2
Total experiments	123	

of fibrogen into the femoral veins and the injections of ink into the foot were made simultaneously. The dogs were killed after twenty hours, and in three of the four there was definite discoloration of the iliac lymph glands. These experiments definitely proved that the lymphatics were permeable, even at the height of the edema. While it is true that the passage of the particles of ink was delayed in the limbs with edema, this is readily explained by the pressure exerted on the lymph vessels by the edema and by the limitation of activity in the edematous leg (table 3).

COMMENT

The experiments described have led to a simple, reliable method of producing edema in the extremity of the dog which is comparable to that seen in man following femoral or iliac thrombophlebitis. Simple ligation of the main veins of the extremity failed to result in such an edema. This, in view of the results of the production of an extensive peripheral obstruction of the veins, indicates that the simple ligation fails because the collateral supply is too readily developed to permit a

considerable degree of venous insufficiency. The production of a localized chemical phlebitis of the iliac veins, with more or less associated periphlebitis, also failed to result in edema of the extremity. The mechanical extirpation of the lymph-bearing tissues did not, in most of the experiments, lead to the development of edema of the corresponding limb. These results indicate that obstruction of the lymphatics does not play a primary rôle in the development of the postphlebitic edemas.

Obliteration or obstruction of the peripheral veins over a sufficiently extensive area in almost every instance was followed by the development of typical phlegmasia alba dolens. Such an obstruction by the injection of the blandest substances possible, even of the animal's own serum, provides little support for the theory of a lymphatic obstruction as the cause of the edema. Finally, the experiments with the injection of india ink definitely proved the patency of the lymphatics, even at the height of the edema. While it is true that the transport of particles of ink was delayed in the edematous limbs, this is readily explained by the pressure exerted on the lymphatics by the edema fluid. Furthermore, it is known that muscular activity is an important factor in furthering the flow in the lymphatics. These greatly swollen limbs are held immobile by the animals, depriving the lymph stream of the pumping action of the muscles.

The duration of the edema was directly proportional to its intensity. In none of the experiments, however, did it last for more than from three and one-half to four and one-half weeks. In this respect, the edemas differed from those of severe human cases of phlegmasia alba dolens in which the swelling may persist indefinitely, or may recur with excessive standing or walking. The transient nature of the edema in the animals is accounted for by several factors. As will be seen in the microscopic preparation (figs. 10 and 11), canalization of the thrombi occurs promptly, and probably results in some measure of restoration of the venous return. The rapid development of collateral circulation, as evidenced by the appearance of dilated superficial veins on the thigh and abdomen, and the enlargement of otherwise inconspicuous deep veins indicate the degree and rapidity of this collateral development. A final factor is seen in the difference in hydrostatic pressure in man as compared with the quadruped. This, plus the much earlier resumption of muscular activity on the part of the dog, probably further favors the early disappearance of the edema.

The rôle of lymphostasis in the thrombophlebitic edemas should not be denied. In the first place, venous obstruction per se increases the flow of lymph, and the rate of transport does not keep pace with the rate of production, as the mechanical pressure of the edema fluid and the immobilization of the edematous limb seriously interfere with the movement of lymph. In later stages of edema, the connective tissue

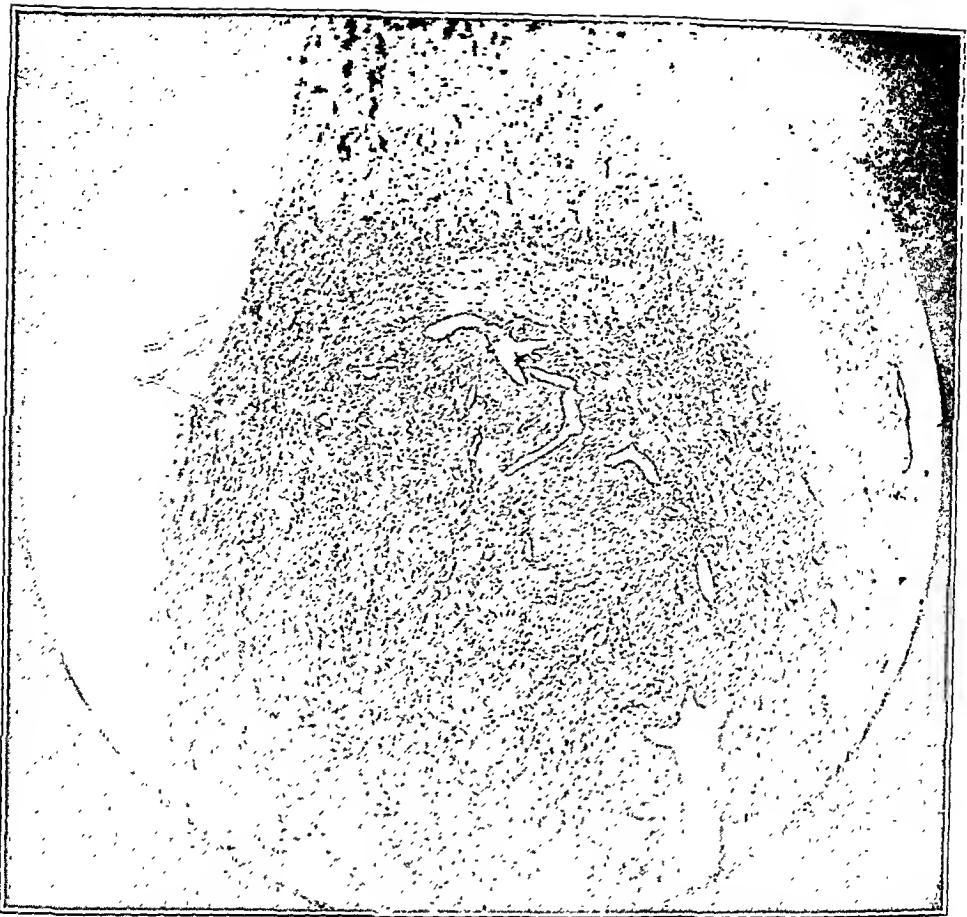


Fig. 10.—Low power photograph after one week, showing obliteration of the femoral vein, and active canalization of the thrombus.

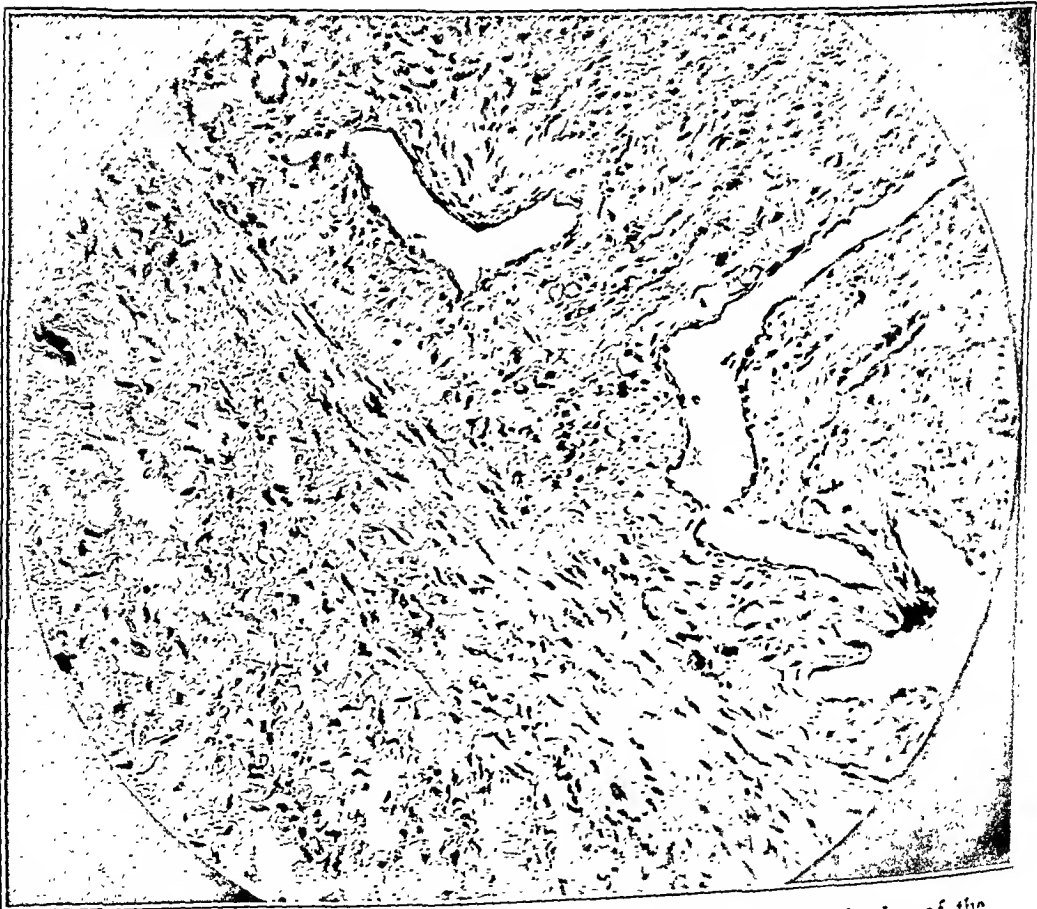


Fig. 11.—High power view of section in figure 9, showing canalization of the thrombus.

reaction, which is the result of the persistence of a protein-rich exudate in the tissues, will strangle the lymph channels and cause a peripheral lymph block. In tissues excised during Kondoleon operations one can uniformly observe such dilated lymphatics.

This secondary lymphostasis, however, has nothing in common with the lymphatic obstruction postulated by Homans and Zollinger, Reichert⁹ and others, who claim a primary obstruction of the perivenous lymph channels and lymph glands in thrombophlebitic edema. Our results fail to confirm their supposition. We are aware of the fact that the chronic edema seen after iliac thrombosis in man presents additional factors that we have not reproduced in the animal, namely, the superimposed infections of the skin, the recurrent attacks of erysipelas with more burden on the lymphatics and the thrombophlebitic ulcers. Also the so-called "idiopathic" edema, without any evidence of venous thrombosis, may have a type of mechanism that is different from the one reproduced here. The extensive venous thrombosis, however, which not only blocks the femoral or iliac veins at one segment, but extends far into the tributaries, closely imitates the condition encountered in deep venous thrombosis in man.

The accumulation of fluid in the tissues cannot be explained purely on the basis of a filtration edema. It is true that when capillary pressure rises above the osmotic pressure of the blood, the flow of fluid from the tissues to the capillaries is reversed. Obviously, there is a great rise in capillary pressure following mechanical obstruction in the veins. The edema, however, which can be observed in normal subjects standing erect and immovable for thirty minutes contains only a small amount of protein: the endothelium is intact and hardly or not at all permeable.¹⁰ The fact that our edema fluids contain high percentages of protein can be interpreted only as a sign of endothelial damage, resulting in increased permeability to the proteins of the blood. The capillary stasis, which deprives the capillary endothelium of sufficient oxygen, is the most probable cause for this leakage of protein. The work of Landis has conclusively shown the great sensitivity of endothelium to even a small diminution of the supply of oxygen.¹¹

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That the edema fluid is rich in protein explains certain characteristics of thrombophlebitic edema. In the first place, it explains why the edema does not disappear as fast as a simple filtration edema, owing to an increase in venous pressure. As long as the increased capillary permeability persists, the exudation of protein-containing fluid will go on. However, when the capillary permeability is restored, it will also become impermeable to the protein in the exudate.¹² The osmotic pressure of this exudate seems also of importance and is now being investigated.

Edema fluids containing protein can be absorbed through the lymphatics, and the experiments of Lewis¹³ showed conclusively that protein is transported along this route. Another mechanism has been pointed out by Landsberg,¹⁴ who observed that protein may be broken down by enzymes produced, no doubt, in adjoining cells. The cleavage products can then be directly absorbed into the blood stream. This might explain the death of some of the experimental animals and the toxic, febrile reactions that occur in acute thrombosis without infection in man.

The hemorrhagic, protein-rich exudate is not indifferent to the tissues. The connective tissue reaction will result in fibrosis and further inhibition of venous and lymphatic transport. We gained the impression in our experiments on animals, that the degree and duration of the edema were related to the height of the protein content and the hemorrhagic character of the fluid. From a clinical standpoint, much will depend on whether the edema can be made to subside rapidly and whether or not the capillary damage is permanent.

The Kondoleon operation, which we practice according to the modification of Sistrunk,¹⁵ may be interpreted in the light of our experiments to act by removing a large amount of diseased, fibrous connective tissue with vacuolar spaces that retain water easily. The removal of the fascia might expose the subcutaneous tissues to a more direct muscular pump action. The working hypothesis that new lymphatic connections drain off the lymphostasis is not tenable, because even if lymphatic block were a primary factor, the iliac lymph glands and channels, which drain the lymphatics of the entire lower extremities, would not be affected by this operation.

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SUMMARY

1. Ligation of the iliac and femoral veins, alone or in all possible combinations with the contralateral veins, did not produce edema in the lower extremities of dogs.

2. A localized chemical phlebitis and periphlebitis induced with strong irritants, such as 50 per cent sodium salicylate and tincture of iodine, produced a segmental thrombosis but no edema of the limb.

3. Removal of the iliac lymph glands together with all of the retroperitoneal fatty and areolar tissues from the bifurcation of the aorta to Poupart's ligament failed to produce edema of the limb even when the common and internal iliac veins were divided at the same time. In several animals the dissection was repeated to remove any regenerated lymphatics and the collateral veins were ligated, but edema did not develop.

4. From 50 to 70 per cent alcohol injected peripherally into the femoral vein caused extensive venous thrombosis extending into the tributaries and a marked edema lasting from two and a half to three and a half weeks.

An emulsion of barium sulphate in gelatin also produced marked edema.

Tissue extracts from muscles of the hearts of dogs, the dogs' own serums and finally a concentrated tissue extract, fibrogen, when injected into the femoral vein, caused an extensive venous thrombosis with marked edema. The edema fluid was hemorrhagic and contained comparatively high percentages of protein, indicating a damage to the capillary endothelium. If the fibrogen was prevented from forming a clot by the simultaneous injection of heparin, there was no edema.

5. In spite of marked edema, particles of india ink, injected into the foot reached the iliac lymph glands, although delayed by the pressure of the fluid and by the limitation of muscular activity.

6. An obstruction of the peripheral veins over a sufficiently extensive area with a bland, noninflammatory clot produced marked edema, with very little and only secondary involvement of the lymphatics. These results do not confirm the results of recent workers, who emphasize lymphatic obstruction.

7. Some clinical applications of these observations are pointed out.

185 North Wabash Avenue.

122 South Michigan Avenue.

THE IMMEDIATE CONTRACTION OF CUTANEOUS GRAFTS AND ITS CAUSE *

JOHN STAIGE DAVIS, M.D.

AND

EDWARD A. KITLOWSKI, M.D.

BALTIMORE

We have often noticed that there is a definite shrinkage in the size of free skin grafts immediately after being cut; this fact has also been recorded in the literature by other observers, but so far as we have been able to ascertain, no one has attempted to measure the exact amount of shrinkage or to compare this shrinkage in the different types of grafts. This report is the result of an investigation to determine the amount of contracture and to explain the probable cause.

In cutting grafts of different thicknesses we found that the shrinkage seemed to vary with the depth at which they were cut. For this reason we selected for measurement areas of skin of different thicknesses: whole thickness, half thickness, thick Ollier-Thiersch and thin or true Ollier-Thiersch grafts.

The whole thickness grafts included the whole thickness of the skin, excluding the hypoderm. The half thickness grafts were cut about half through the corium. The thick Ollier-Thiersch grafts were cut with the aid of Blair's suction boxes and included the papillae of the corium. The true Ollier-Thiersch grafts, which are the thinnest that can be cut, were also obtained with the aid of Blair's suction boxes and included the epidermis and the tips of the papillae of the corium (fig. 1).

HISTOLOGIC ANATOMY

The skin consists of three layers: epidermis, dermis or corium, and the hypodermis or subcutaneous layer. The epidermis is a nonvascular covering composed of pavement epithelial cells. The dermis or corium is made up of dense fibrous tissue with strands of yellow elastic tissue. It contains the blood vessels, lymphatics, nerves, touch follicles and hair follicles and some of the oil and sweat glands. The hypodermis consists of bundles of loose connective tissue containing masses of fat cells in their meshes. Most of the sweat glands and the deep hair follicles also lie in this layer.

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* From the Surgical Department of the Johns Hopkins University and Hospital, Division of Plastic Surgery.

The epidermis is divided into four layers of cells: the stratum corneum, stratum lucidum, stratum granulosum and stratum mucosum (fig. 1).

The stratum corneum consists of several layers of flattened non-nucleated cells, the more superficial of which assume the form of horny

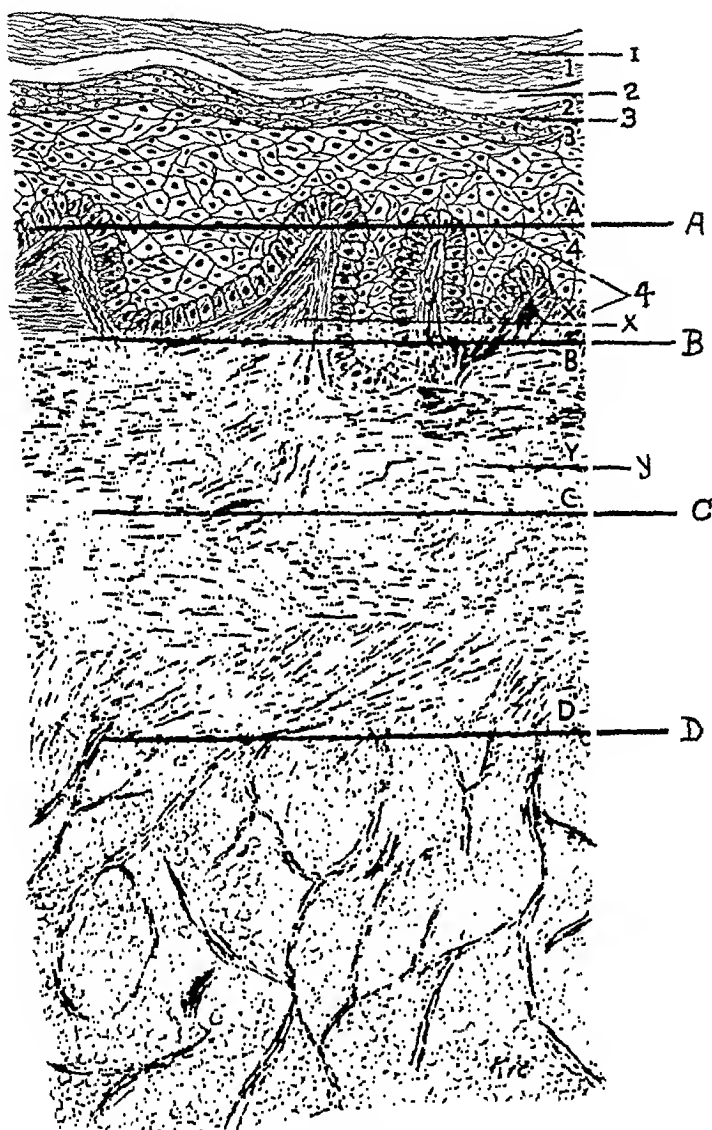


Fig. 1.—Schematic drawing of a vertical section of the skin. 1 indicates the stratum corneum; 2, stratum lucidum; 3, stratum granulosum; 4, stratum mucosum; A, level at which the true Ollier-Thiersch grafts were cut; B, level at which the thick Ollier-Thiersch grafts were cut; C, level at which the half thickness grafts were cut; D, level at which the whole thickness grafts were cut; X, papillary layer of the corium; Y, reticular layer of the corium.

scales, which are gradually removed by friction. The stratum lucidum consists of an apparently homogeneous layer of flattened cells which con-

tain granules of keratohyalin. The stratum granulosum consists of three or four layers of flattened cells around the nuclei of which are granules of eleidin, a substance that apparently represents an intermediate stage between the protoplasm of the deeper cells and the keratin of the superficial layers. The stratum mucosum consists of several parts: a basal layer or the stratum germinativum, consisting of one or two layers of cylindrical cells with large nuclei, standing on a basement membrane, and above these cells several layers of prickle cells united to each other by filamentous processes.

The corium is divided into two parts: the pars papillaris or papillary layer and the pars reticularis or reticular layer.

The papillary layer, which consists of fine fibrous tissue with some elastic tissue, is thrown into ridges that are covered by the overlying mucous layer of the epidermis. These folds are called papillae. They afford favorable positions for the lodgment of the terminal capillaries and special organs of touch. The papillae are best developed on the flexor surfaces of the hands and feet, and they do not vary throughout life.

The reticular layer is a continuation of the papillary layer. In this layer the fibrous and elastic tissue is more closely interlaced, and it is the "leather" of the skin.

The general course of the fibrous bundles within the corium is parallel or oblique to the surface. Some strands come upward vertically from the subcutaneous layer below, traverse the reticular layer and either bend over the fibrous bundles in this layer and go down again or join these bundles. The bundles that are best developed have a direction parallel with the usual lines of tension of the skin; hence wounds of the skin that are at right angles to these lines tend to gape most. The bundles take a direction nearly at right angles to the long axis of the limbs; they run obliquely on the trunk and caudally and laterally from the spine. Their direction on the face and neck can best be seen in the illustration (fig. 2). The lines of tension of the skin are called the lines of Langer.

The elastic tissue, which constitutes a considerable portion of the corium, occurs as fibers and networks (fig. 3). In the reticular stratum they form strong bundles, corresponding with the general arrangement of the fibrous tracts. Toward the surface of the corium, the elastic fibers become finer and more branched and anastomose beneath the epidermis, forming a fine subepithelial elastic network.

These elastic fibers unquestionably determine the shrinkage of cutaneous grafts after the grafts have been cut, and this shrinkage will depend on the depth at which they were cut. If the whole thickness of the skin is taken, the shrinkage will be maximum. whereas if only the

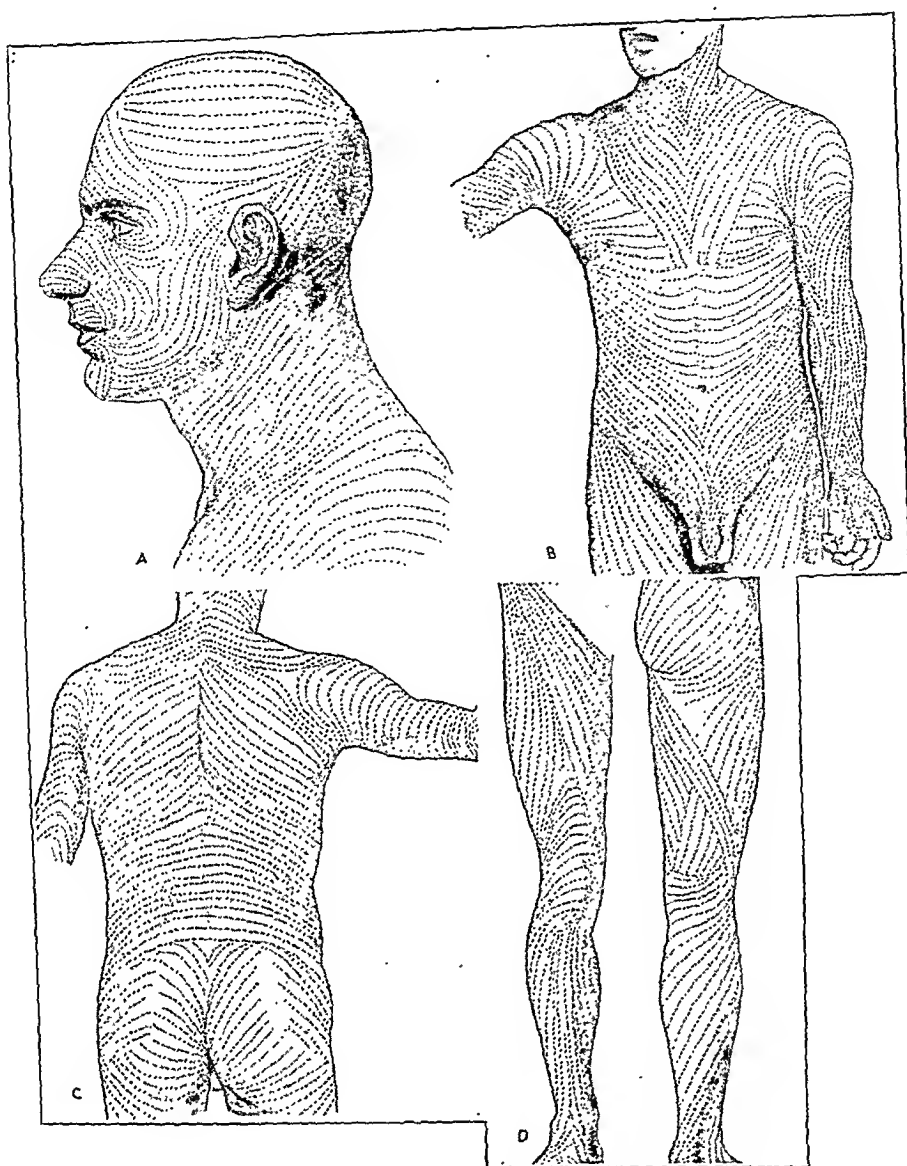


Fig. 2.—These illustrations, *A*, *B*, *C* and *D*, show the lines of normal tension of the skin known as the lines of Langer. Incisions through the skin across these lines will gape wider than those cut parallel to them, and incisions closed parallel to these lines will be less likely to cause wide scars than those closed across them. The elastic tissue of the corium throws the papillary layer into definite folds which cause these patterns. The epithelium plays no part in the formation of these folds, as it merely covers the corium beneath. These patterns are practically uniform, with only minor individual variations. This illustration is redrawn from Kirschner and Schubert (*Allgemeine und spezielle chirurgische Operationslehre*, Berlin, Julius Springer, 1927, vol. 1, p. 326). *A* shows Langer's lines of normal skin tension on the head and neck; *B*, Langer's lines of normal skin tension on the front of the trunk and upper extremity; *C*, Langer's lines of normal skin tension of the back of the trunk and buttocks; *D*, Langer's lines of normal skin tension on the front and back of the thigh and leg.

epidermis and the papillary layer are taken, as in a deep Ollier-Thiersch graft, then the shrinkage will be much less. A graft that does not include any of the corium, or only the tips of the papillae and the epidermis, should have no shrinkage, except the slight amount due to the natural contraction of the cells themselves.

TECHNIC

The following procedures were used in measuring the grafts before and after cutting:

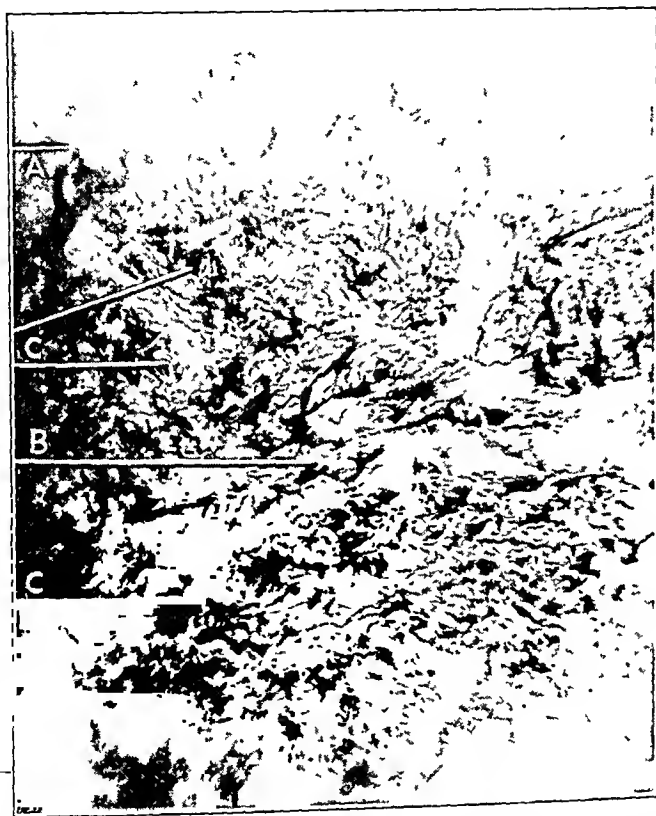


Fig. 3.—Photomicrograph of a section of a whole thickness graft stained with Weigert's stain to bring out the elastic fibers of the corium. No counter-stain. *A* indicates epithelium; *B*, corium; *C*, elastic fibers which take a very deep stain.

Sterilized perforated cellosilk and 5 per cent brilliant green in alcohol are the materials used in securing the measurements. Where whole thickness and half thickness grafts are to be measured, the size of the graft desired is carefully outlined on the cellosilk with the brilliant green applied with the point of a toothpick. This outline, which is the exact size of the graft desired and also of the graft before cutting, is placed on the area from which the graft is to be taken and reoutlined with brilliant green; the dye passing through the perforations in the cellosilk leaves a dotted pattern on the skin. These dots are then connected, and the outline is thus marked on the skin. The graft is then removed and flattened

out on another piece of cellosilk, care being taken not to stretch it. A second tracing is then made, which gives the area of the graft after shrinkage has taken place.

A different procedure had to be used in obtaining the measurement of the shrinkage in thick and true Ollier-Thiersch grafts, because the margins of these grafts could not be accurately cut in a given pattern, and because the thick Ollier-Thiersch grafts always tapered into true Ollier-Thiersch grafts at the edges. In order to overcome this difficulty, a square with sides about 2.5 cm. long is made on the cellosilk and transferred to the skin in the center of the area from which the graft is to be cut. After cutting, the thick or the true Ollier-Thiersch graft is carefully spread on a board covered with protective tissue. The area previously marked out is then traced on a second piece of cellosilk, which gives the size of the square after shrinkage has taken place.

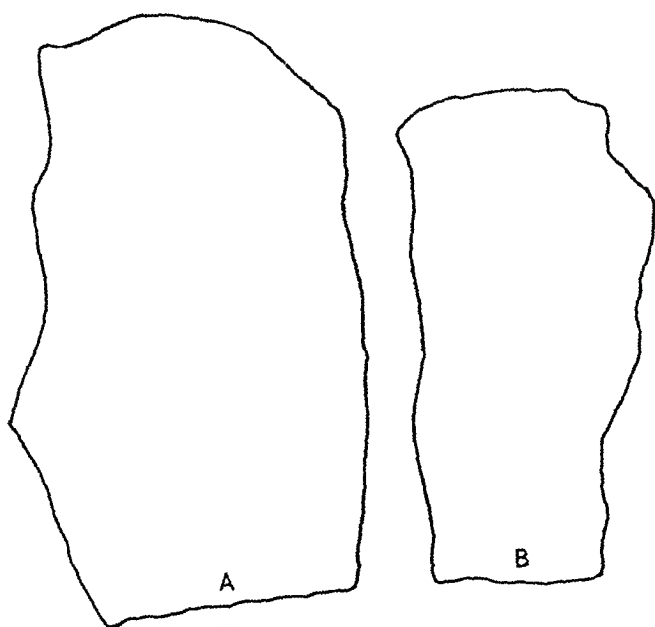


Fig. 4.—Outlines of a whole thickness graft taken from the abdominal wall of a man, aged 40 (table 1, case 15), who had a roentgen ray burn of the skin over the knee, which was excised and skin-graft applied. *A* shows the tracing made before cutting the graft; area, 29.0982 sq. cm. *B* shows the tracing made after cutting the graft; area, 16.4084 sq. cm. There was a shrinkage of 12.6898 sq. cm., or 43.61 per cent. Note the same general outline, which is much smaller in *B* because of the immediate shrinkage. (The original outlines have been reduced one half).

The tracings are then transferred to sheets of paper and the areas computed by means of a planimeter. The difference in the areas of each pair of tracings shows the shrinkage for that particular graft. As all the grafts are of different sizes, we used the percentage of shrinkage as a method of comparison (figs. 4, 5, 6 and 7).

The following tables were compiled from tracings secured by the procedure described. All of the grafts measured were obtained and transplanted by us in the course of routine work. The planimeter readings and the computations were made by one of us in order to make them as uniform as possible.

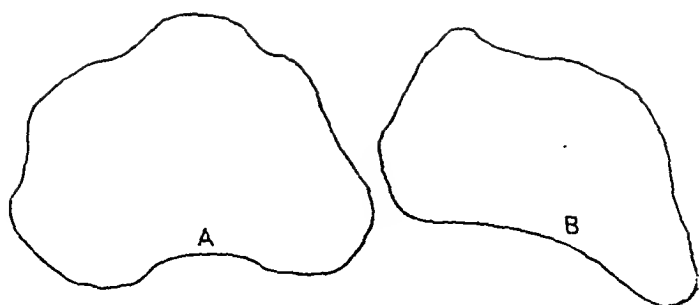


Fig. 5.—Outlines of a half thickness graft taken from the abdominal wall of a girl, aged 10 (table 2, case 2) who had a contracted scar from a burn which was released and grafted. *A* shows tracing before cutting; area, 6.5430 sq. cm. *B* shows tracing after cutting; area, 5.0323 sq. cm. There was a shrinkage of 1.5107 sq. cm., or 23.09 per cent. Note that the general outline is about the same and that the shrinkage is less than in the whole thickness grafts. (The original outlines have been reduced one-half.)

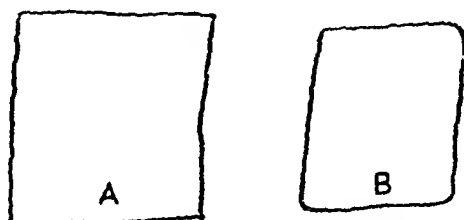


Fig. 6.—Outlines of a thick Ollier-Thiersch graft taken from the thigh of a man, aged 38 (table 3, case 13) who had a roentgen ray burn of the cheek, which was excised and skin-graft applied. *A* shows tracing made on the skin in the central part of the area taken in the graft; area, 4.3210 sq. cm. *B* shows tracing of *A* after the graft was cut; area, 3.7430 sq. cm. There was a shrinkage of 0.5780 sq. cm., or 13.60 per cent. (The original outlines have been reduced one fourth of an inch.)

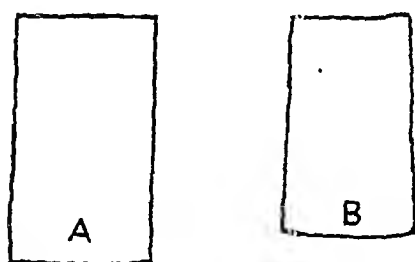


Fig. 7.—Outlines of a true Ollier-Thiersch graft taken from the thigh of a boy, aged 16 (table 4, case 8) who had granulating areas on both ears due to a burn. *A* shows tracing before cutting graft; area, 2.5411 sq. cm.; *B*, tracing after cutting graft; area, 2.5096 sq. cm. There was a shrinkage of 0.0315 sq. cm., or 1.23 per cent.

RESULTS OBTAINED WITH THE VARIOUS TYPES OF GRAFTS

Whole Thickness Grafts.—In this series of twenty there were twelve males and eight females. The variation in age was from 3 to 50 years. Nine grafts were taken from the abdominal wall; seven from the thigh.

and four from the arm. The area of the largest graft before cutting was 30.6425 sq. cm. and the largest area after cutting was 17.2288 sq. cm. The area of the smallest graft was 1.6256 sq. cm. before cutting and 0.9144 sq. cm. after cutting. The largest amount of shrinkage was 44 per cent and the smallest 43.01 per cent, with an average shrinkage of

TABLE 1.—Whole Thickness Grafts

Num- ber	Sex	Age	Source of Graft	Area of Tracing, Sq. Cm.	Area of Free Graft, Sq. Cm.	Amount of Shrinkage, Sq. Cm.	Percentage of Shrinkage
1	Female	5	Abdominal wall	5.9900	3.9370	3.0530	43.67
2	Male	3	Abdominal wall	4.5110	2.5349	1.9761	43.86
3	Male	30	Abdominal wall	28.5699	16.0528	12.5171	43.80
4	Female	10	Abdominal wall	21.9562	12.3952	9.5910	43.63
5	Female	10	Thigh	14.9733	8.5344	6.4389	43.74
6	Female	46	Abdominal wall	10.3632	5.9050	4.4582	43.01
7	Female	6	Thigh	11.7856	6.6522	5.1334	43.56
8	Female	18	Arm	2.0320	1.1379	0.8940	44.00
9	Male	38	Thigh	2.6416	1.4935	1.1480	43.47
10	Male	28	Abdominal wall	14.2240	7.9781	6.2458	43.91
11	Male	50	Thigh	30.6425	17.2288	13.4137	43.78
12	Female	32	Thigh	3.5763	2.0370	1.5392	43.04
13	Male	24	Arm	3.1496	1.7780	1.3716	43.54
14	Male	37	Thigh	2.0726	1.1785	0.8940	43.13
15	Male	40	Abdominal wall	29.0952	16.4054	12.6898	43.61
16	Male	3	Abdominal wall	1.6256	0.9144	0.7112	43.75
17	Male	42	Abdominal wall	28.0822	15.7556	12.3266	43.89
18	Male	7	Thigh	1.6662	0.9372	0.7289	43.75
19	Female	22	Arm	6.2763	3.5585	2.7178	43.30
20	Male	18	Arm	3.8070	1.8643	1.4427	43.62

Average amount of shrinkage, 43.60 per cent.

TABLE 2.—Half Thickness Grafts

Num- ber	Sex	Age	Source of Graft	Area in Tracing, Sq. Cm.	Area in Free Graft, Sq. Cm.	Amount of Shrinkage, Sq. Cm.	Percentage of Shrinkage
1	Male	12	Thigh	3.6472	2.7354	0.9118	25.00
2	Female	10	Abdominal wall	6.5430	5.0322	1.5107	23.09
3	Male	19	Arm	2.3241	1.7433	0.5808	24.99
4	Female	21	Thigh	4.9479	3.7364	1.2115	24.48
5	Male	30	Arm	2.0144	1.5146	0.4998	24.81
6	Female	21	Arm	2.5963	1.9878	0.6085	23.45
7	Female	21	Thigh	2.1513	1.5918	0.5595	26.00
8	Male	34	Abdominal wall	6.2445	4.6052	1.6393	25.70
9	Male	10	Thigh	2.6299	2.0092	0.6207	23.60
10	Female	21	Thigh	3.9870	2.9735	1.0135	25.42
11	Female	24	Arm	1.2159	0.9177	0.3012	24.71
12	Male	12	Thigh	5.2503	3.9156	1.3352	25.42
13	Female	45	Thigh	1.2245	0.9409	0.2836	23.17
14	Female	24	Arm	2.1716	1.6380	0.5336	24.57
15	Male	15	Abdominal wall	2.8072	2.0871	0.7201	25.65
16	Male	43	Thigh	3.7411	2.7801	0.9510	25.42
17	Female	30	Thigh	1.6723	1.2720	0.4003	23.93
18	Male	29	Arm	2.4191	1.8017	0.6174	25.52
19	Female	45	Thigh	1.8691	1.3820	0.4871	26.06
20	Male	32	Arm	1.6700	1.2389	0.4311	25.81

Average amount of shrinkage, 24.84 per cent.

43.60 per cent. The average amount of shrinkage in the grafts taken from the abdominal wall was 43.70 per cent; from the thigh, 43.49 per cent, and from the arm, 43.61 per cent. According to our findings therefore, a whole thickness graft shrinks a little less than half immediately after it is cut.

Half Thickness Grafts.—In this series of twenty there were ten males and ten females. The ages ranged from 3 to 45 years. Ten, or

half of the grafts were taken from the thigh; three from the abdominal wall, and seven from the inner side of the arm. The area of the largest graft was 6.5430 sq. cm. before cutting and 5.0323 sq. cm. after cutting. The area of the smallest graft was 1.2189 sq. cm. before cutting and 0.9177 after cutting. The largest amount of shrinkage was 26.6 per cent and the smallest, 23.09 per cent, with an average of 24.84 per cent. The average amount of shrinkage for the grafts removed from the abdominal wall was 24.81 per cent; from the thigh 24.85 per cent, and from the arm 24.83 per cent. It was impossible to cut the grafts at a uniform depth, which probably accounts for some of the shrinkage. Half thickness grafts have an immediate shrinkage of about one-fourth after being cut.

TABLE 3.—*Thick Ollier-Thiersch Grafts*

Num- ber	Sex	Age	Source of Graft	Area in Tracing, Sq. Cm.	Area in Free Graft, Sq. Cm.	Amount of Shrinkage, Sq. Cm.	Percentage of Shrinkage
1	Male	10	Thigh	3.9194	3.5077	0.4117	10.51
2	Male	21	Thigh	2.7625	2.4476	0.3150	11.38
3	Female	15	Thigh	3.3995	3.1351	0.2644	7.77
4	Female	8	Thigh	4.2463	3.5989	0.6474	15.24
5	Female	17	Thigh	3.2771	2.9198	0.3578	10.91
6	Male	29	Abdominal wall	4.3606	3.8834	0.4772	10.94
7	Male	24	Abdominal wall	3.5194	3.1264	0.3930	11.16
8	Male	21	Thigh	3.9197	3.4187	0.5060	12.90
9	Female	17	Thigh	2.0546	1.8192	0.2354	11.45
10	Female	36	Thigh	3.0604	2.7117	0.3487	13.72
11	Female	30	Thigh	3.7909	3.1686	0.6223	16.41
12	Female	17	Thigh	3.5447	3.1414	0.4033	11.37
13	Male	38	Thigh	4.3210	3.7430	0.5780	13.60
14	Female	36	Thigh	2.8336	2.6098	0.2238	11.45
15	Male	24	Abdominal wall	3.4949	3.0995	0.3954	10.50
16	Female	17	Thigh	2.2289	1.9610	0.2679	12.01
17	Male	52	Thigh	3.1046	2.8488	0.2558	8.23
18	Male	29	Abdominal wall	3.5648	3.1341	0.4307	12.09
19	Female	19	Thigh	3.7566	3.2857	0.4709	12.53
20	Female	17	Thigh	2.5913	2.2874	0.3039	11.72
Average amount of shrinkage, 11.81 per cent.							

Thick Ollier-Thiersch Grafts.—In this series of twenty there were nine males and eleven females. The variation in age was from 8 to 52 years. Four grafts were taken from the abdominal wall and the remainder, or 16, from the thigh. The area of the largest graft was 4.3606 sq. cm. before cutting and 3.8834 sq. cm. after cutting. The area of the smallest graft before cutting was 2.0546 sq. cm. and 1.8192 sq. cm. after cutting. The largest amount of shrinkage was 16.41 per cent and the smallest 7.77 per cent. There is a greater variation here than in the other types of grafts. This, we think, is due to the method of cutting, which precludes the possibility of securing grafts of absolutely uniform thickness. If case 2 and case 6 were not considered, the difference would not be so great, and the average for the series would be 12.23 per cent instead of 11.81 per cent, with the majority of the cases falling between 10 and 13 per cent. The average amount of shrinkage for the grafts removed from the abdominal wall was 11.26 per cent and from the thigh, 11.95 per cent.

True Ollier-Thiersch Grafts.—In this series of twenty there were eight females and twelve males. The variation in age was from 8 to 51 years. Three grafts were taken from the abdominal wall and the remaining seventeen from the thigh. The area of the largest graft before cutting was 3.0556 sq. cm. and 3.0353 sq. cm. after cutting. The area of the smallest graft was 1.0160 sq. cm. before cutting and 1.007 sq. cm. after cutting. The largest amount of shrinkage was 2.00 per cent, and the smallest was 0.51 per cent, with an average of 1.24 per cent. The average amount of shrinkage in the grafts taken from the abdominal wall was 1.08 per cent and in those taken from the thigh, 1.27 per cent. This shrinkage is due partly, perhaps, to a normal contracture of the

TABLE 4.—*True Ollier-Thiersch Grafts*

Num- ber	Sex	Age	Source of Graft	Area in Tracing, Sq. Cm.	Area in Free Graft, Sq. Cm.	Amount of Shrinkage, Sq. Cm.	Percentage of Shrinkage
1	Female	20	Thigh	1.9753	1.7640	0.2113	1.06
2	Female	18	Thigh	1.7881	1.7576	0.0305	1.70
3	Male	30	Abdominal wall	2.4460	2.4333	0.0127	0.51
4	Female	10	Thigh	2.1207	2.0955	0.0152	0.72
5	Male	51	Thigh	2.9067	2.9184	0.0482	1.62
6	Female	20	Thigh	1.6908	1.4457	0.2451	1.45
7	Male	30	Abdominal wall	2.2326	2.1971	0.0355	1.59
8	Male	16	Thigh	2.5411	2.5096	0.0315	1.23
9	Female	21	Abdominal wall	2.4079	2.3799	0.0279	1.16
10	Male	10	Thigh	1.0160	1.0007	0.0153	1.50
11	Male	51	Thigh	2.5542	2.5034	0.0508	1.11
12	Female	10	Thigh	1.9050	1.8669	0.0381	2.00
13	Male	26	Thigh	2.1543	2.1023	0.2520	1.16
14	Male	14	Thigh	2.5679	2.5501	0.0177	0.69
15	Male	24	Thigh	1.8288	1.8103	0.0185	1.01
16	Female	8	Thigh	3.0556	3.0353	0.0203	0.66
17	Male	26	Thigh	1.6687	1.6357	0.0330	1.98
18	Male	10	Thigh	1.4680	1.4351	0.0431	1.73
19	Male	16	Thigh	2.3476	2.2193	0.2183	0.92
20	Female	18	Thigh	1.7475	1.5448	0.2027	1.16

Average amount of shrinkage, 1.24 per cent.

cells, but principally to errors made in copying the tracings. Theoretically, there should be no measurable shrinkage in these grafts since there is little or no elastic tissue in them, and the contraction of the cells would be very slight. Therefore, the whole shrinkage could be considered as an error in manipulation.

COMMENT

Whole thickness grafts, which shrink most, contain all the elastic tissue, with the exception of a few bundles that dip down into the hypoderm. Half thickness grafts, cut through the reticular layer of the corium, contain less elastic tissue, since we attempted to leave about half of the corium, and consequently they shrink less. Thick Ollier-Thiersch grafts, which included the papillae of the corium and which therefore

contained only fine elastic tissue in a looser network than the reticular layer below, shrink still less. True Ollier-Thiersch grafts, which include the epidermis and only the tips of the papillae of the corium, contain little or no elastic tissue and practically do not shrink as compared with the other types of grafts. From these observations, we feel justified in assuming that the elastic tissue in the fibrous bundles is the cause of the shrinkage.

Sections were stained with Weigert's stain, which is a stain for elastic tissue only, and these sections clearly indicated the varying

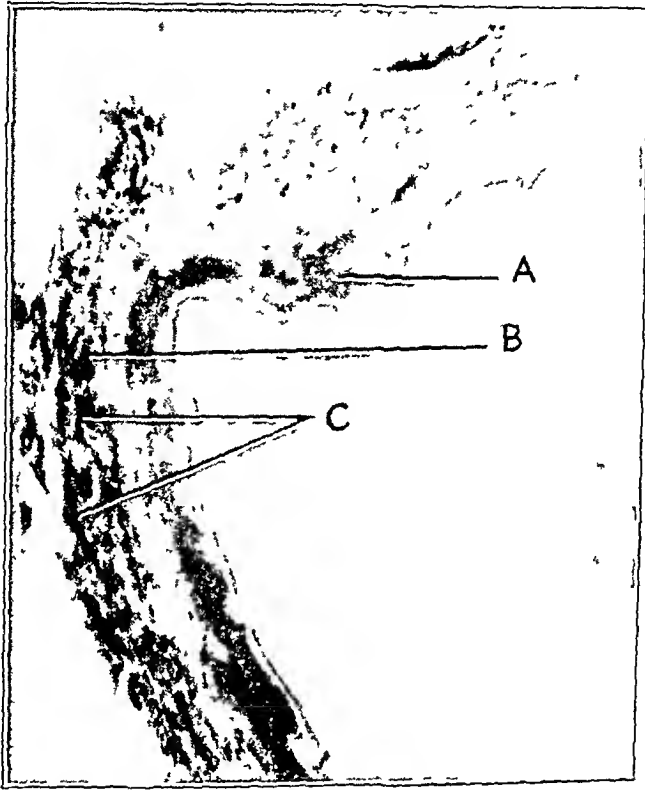


Fig. 8.—Photomicrograph of a section of a half thickness graft stained with Weigert's stain to bring out the elastic tissue. *A* indicates epidermum; *B*, corium; *C*, elastic fibers.

amounts of elastic tissue in the different grafts (figs. 3, 8 and 9). The sections of the true Ollier-Thiersch grafts did not show elastic tissue.

Age apparently plays no part in the amount of shrinkage of the grafts. Our series included patients whose ages ranged from 3 to 52 years, and there was no definite difference in the results.

The grafts were irregular in shape in order to fill the various defects for which they were cut, and so they could not be taken in the lines of normal tension of the skin. However, the shrinkage appeared to be the same in all directions, as after cutting the grafts retained the shape of the original patterns to a large extent. Furthermore, the shrinkage appears to be about the same in grafts taken from different parts of the

body. Grafts from the arm were taken from the upper inner side of the arm. Grafts from the abdominal wall were usually taken from the lower right or left quadrants, and the grafts from the thigh were usually taken from the upper half of the anterior portion.

CONCLUSIONS

The only variable factor in these grafts is the amount of corium with its elastic tissue. The whole thickness grafts including all of the elastic tissue showed the largest amount of shrinkage, which was 43.60 per cent. The half thickness grafts consisting of only a portion of the

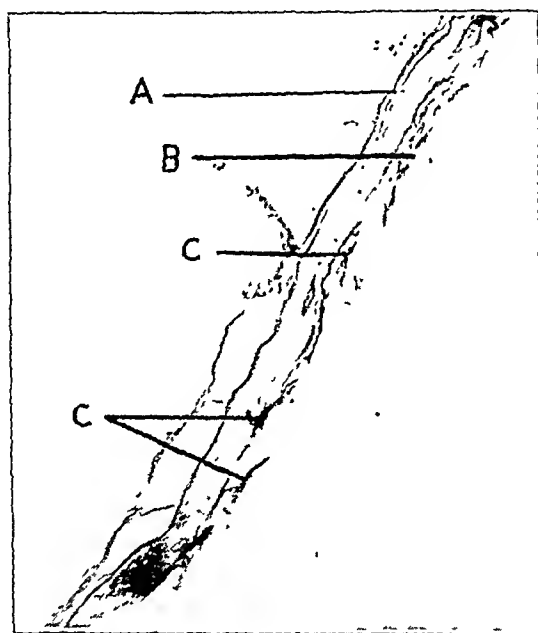


Fig. 9.—Photomicrograph of a section of a thick Ollier-Thiersch graft stained with Weigert's stain to bring out the elastic tissue. *A* indicates epithelium; *B*, papillae of the corium; *C*, elastic fibers.

corium with about half of its elastic tissue showed a shrinkage of 24.86 per cent. The thick Ollier-Thiersch grafts containing only the finest network of elastic tissue of the papillary layer of the corium had a shrinkage of 11.81 per cent. The true Ollier-Thiersch grafts which contained only the tips of the papillae of the corium and no elastic tissue had a shrinkage that ranged up to 2 per cent, which might well be considered an error of manipulation.

If this percentage of error is subtracted from the other three results, we feel justified in saying that whole thickness grafts have a shrinkage of 41 per cent; half thickness grafts, 22 per cent, and thick Ollier-Thiersch grafts, 9 per cent, while true Ollier-Thiersch grafts have no actual shrinkage.

THE RELEASE OF PERICARDIAL ADHESIONS*

HUGH H. TROUT, M.D.

ROANOKE, VA.

A review of the literature shows that the operations for the release of pericardial adhesions have been rather arbitrarily divided into two types: (*a*) operations that relax the adhesions between the pericardium and the surrounding structures, and (*b*) operations that remove a portion of the leather-like pericardium from around the heart and release the adhesions between the pericardium and the heart, if any such adhesions are present. The more one studies the question of adhesions of the pericardium, the more one is convinced that these two types are but the continuation of the same process. It is unfortunate that custom has divided these operations so that they appear as designed for two different diseases, when, in reality, they are designed to meet different stages of the same process. It is still more unfortunate that the names of men should have become attached to these operations. The following is a partial list of the many confusing terms found in the literature: boning of the wall of the chest for adhesive pericarditis, cardiolysis, Brauer's operation, cardiolysis for mediasternopericarditis, pericardiolysis, Rehn's operation, decortication of the heart, Delorme's operation, Schmieden's operation, pericardial resection, the relief of obstruction to circulation in a case of chronic constrictive pericarditis, precordial resection of the rib for adhesive pericarditis, resection of the pericardium in concretion, resection of the pericardium in accretion, precordial thoracotomy, lysis of intrapericardial adhesions, thoracolysis praecordiacae, and Sauerbruch's operation.

The term "cardiolysis," from its derivation ("kardio," heart; "lysis," loosening), should include all those procedures that have to do with the loosening of the heart, but usage confines this term to operations for removal of the cartilaginous and bony obstructions to the cardiac impulse in cases of chronic mediastinopericarditis. For many years, adherent pericarditis has been found at postmortem examinations. It has been diagnosed correctly by clinicians and ineffectively treated by various drugs, as only temporary relief can be obtained by the employment of habit-forming drugs and cardiac rest.

Churchill¹ quoted Wiell as saying the following in 1895:

After the adhesions have reached a fibrous stage, they act independently of their original cause, and medical therapy is illusory. One has never dreamed of

* Submitted for publication, Dec. 26, 1930.

1. Churchill, E. D.: Decortication of the Heart (Delorme) for Adhesive Pericarditis. *Arch. Surg.* 19:1457 (Dec.) 1929.

attempting a debridement in such a case, less perhaps from resignation than from the uncertainty of diagnosis. There would be good cause to make an attempt of this kind, designed to liberate a part of the heart, the apex for example, and the anterior surface It will one day come within the province of surgery to deliver the heart from the shell which strangles it.

In 1898, Delorme² stated in detail the operation that he thought should be done for the release of adhesions between the heart and the pericardium. This is now known essentially as Delorme's operation for decortication of the heart.

At the meeting of the American Medical Association in 1901, as a part of a symposium on pericarditis, Dr. Babcock³ read a paper on "Adherent Pericarditis." During the discussion following this symposium, Dr. Carl Beck is quoted as having said: "I should like to ask Dr. Babcock as to the advisability, in cases of adherent pericarditis, of approaching the adhesions with the surgeon's knife." As far as I can ascertain, this is the first time the question of application of surgical measures for the relief of symptoms due to adherent pericarditis was raised in America. From this quotation, it must be concluded that Dr. Beck was most indefinite as to the method of applying "the surgeon's knife."

It remained for Rehn⁴ in 1913 to carry out Delorme's theories. Rehn's four patients were unfortunately selected, as two of them were tuberculous and the other two, though benefited, lived only two years following the operation.

Even before Rehn⁴ attempted to carry out Delorme's theories, Brauer,⁵ professor of medicine at Marburg, evidently realized that so formidable an operation would never be popular, so he proposed to Petersen⁶ the removal of the ribs and cartilages that were resisting the apparent systolic beat and diastolic tug at the apex. This operation is now generally known as Brauer's cardiolysis operation for the release of chronic mediastinopericardial adhesions.

In 1907, Wenckbach⁷ performed the first operation of the Brauer type done in England. In 1912, Summers⁸ performed the first operation of this type done in America, for adherent pericarditis.

A review of the literature up to January, 1930, shows that the operation of decortication of the heart for adherent pericarditis has been done, or attempted, in thirty-seven cases. Table 1 is a partial copy of Churchill's complete review. To this list I have added one

2. Delorme, E.: *Gaz. d. hôp.* **71**:1150, 1898.

3. Babcock, Robert H.: *J. A. M. A.* **37**:1578 (Dec. 14) 1901.

4. Rehn, L.: *Berl. klin. Wchnschr.* **1**:241, 1913.

5. Brauer, L.: *München. med. Wchnschr.* **4**:982, 1902.

6. Brauer, L.: *Arch. f. klin. Chir.* **71**:258, 1903.

7. Wenckbach, K. F.: *Brit. M. J.* **1**:63 (Jan. 12) 1907.

8. Dum, A. D., and Summers, J. E.: *Am. J. M. Sc.* **145**:74, 1913.

TABLE 1.—*Results in Forty-three Cases Following Decortication of the Heart for Adherent Pericarditis*

Author	Age	Result
1. Rehn: Berl. klin. Wchnschr. 1:241, 1913	..	Excellent but temporary; tuberculous
2. Rehn: Med. Klin. 16:234, 1920.....	6	Excellent but temporary; tuberculous
3. Rehn: Berl. klin. Wchnschr. 1:241, 1913	13	Excellent; died of rheumatic fever
4. Rehn: Ibid.....	14	Excellent; died 1½ years later of influenza
5. Sauerbruch: Die Chirurgia der Brustorgane, Berlin, Julius Springer, 1925, vol. 2.....	28	Excellent; well for 11 years
6. Sauerbruch: Ibid.....	21	Died 18 days after operation of cardiac insufficiency
7. Sauerbruch: Ibid.....	28	Died 24 days after operation of cardiac insufficiency
8. Sauerbruch: Ibid.....	39	Excellent; died in four years; renal tuberculosis
9. Volhard and Schmieden: Klin. Wchnschr, 2:5, 1923.....	..	Right ventricle torn; operation not completed
10. Volhard and Schmieden: Ibid.....	..	Right ventricle torn; operation not completed
11. Volhard and Schmieden: Ibid.....	..	Right ventricle torn; operation not completed
12. Volhard and Schmieden: Ibid.....	..	Weak girl; died soon after operation
13. Volhard and Schmieden: Ibid.....	..	Weak boy; died 14 days after operation of tuberculosis
14. Volhard and Schmieden: Ibid.....	..	Died; postmortem examination showed heart still encased
15. Volhard and Schmieden: Ibid.....	30	Excellent; patient well for 4 years
16. Volhard and Schmieden: Ibid.....	46	Excellent; patient well for 4 years
17. Schmieden: Zentralbl. f. Chir. 51:46, 1924	22	Died in 3 weeks
18. Schmieden and Fischer: Ergebn. d. Chir. u. Orthop. 19:98, 1926.....	18	Excellent
19. Schmieden and Fischer: Ibid.....	18	Died on table
20. Schmieden and Fischer: Ibid.....	..	Improved
21. Schmieden and Fischer: Ibid.....	5	Improved
22. Bittroff: München. med. Wchnschr. 71:517, 1924	..	Improved; Talma's operation later
23. Delagenière: Gaz. d. hôp., 1913, vol. 86....	28	Improved
24. Guleke and Lommel: Klin. Wchnschr. 4:737, 1925
25. Kirschner and Matthes: Deutsche med. Wchnschr. 52:221, 1926.....	27	Excellent
26. Koennecke: München. med. Wchnschr. 74:675, 1927.....	22	Excellent
27. Koennecke: Ibid.....	21	No improvement
28. Grote: Mitt. n. d. Grenzgeb. d. Med. u. Chir. 38:556, 1925	9	Excellent
29. Ljungdahl and Tengwall: Acta chir. Scandinav. 59:480, 1926.....	20	Excellent
30. Enderlen: Zentralbl. f. Chir., 1925, p. 589	46	Excellent
31. Lillenthal: Thoracic Surgery, Philadelphia, W. B. Saunders Company, p. 422.....	19	Improved for 3 months; died
32. Hanebuth and Naegeli: Med. Klin. 23:1253, 1927	31	Calcified pericardium; slow recovery
33. Laven and Matthes: Deutsche med. Wchnschr., 1928, vol. 54.....	..	Died 1 hour after operation
34. Cutler and Beck in Nelson's Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons.....	24	Improved
35. Churchill: Arch. Surg. 19:1457 (Dec.) 1928	..	Died 1 hour after operation
36. Delorme and Hallopeau: Progrès méd., 1924, p. 457	18	Excellent
37. Delorme and Hallopeau: Ibid.....	16	Excellent
38. Author's case.....	7	Recovery
39. Bigger: Personal communication, 1930...	29	Striking improvement for days; died of tuberculosis
40. Bigger: Ibid.....	25	Good cardiac result in spite of tuberculous peritonitis
41. Whittemore: Arch. Surg. 21:1059 (Dec.) 1930	36	Died 12 hours after operation due to injury to right ventricle
42. Beck and Griswold: Arch. Surg. 21:1064 (Dec.) 1930.....	..	Excellent
43. Eloesser: Arch. Surg., Dec., 1930, vol. 1...	13	Excellent
	..	Died in 4 months of tuberculosis

case of my own, two from the service of Dr. I. A. Bigger, formerly of the Vanderbilt University, one from the service of Dr. Wyman Whittemore, one reported by Beck and Griswold and one by Dr. Leo Eloesser.

From table 1 it will be seen that in the forty-three cases there were eight operative deaths; in nine cases the operation was not completed

In addition to these cases, Kob⁹ reported twelve cases in children. While his results were excellent, he expressed the belief that the more extensive operation of Delorme might have to be done later in some of the cases. He reported no deaths.

In 1907, Danielsen¹⁰ reported nine cases and was much impressed with the necessity of careful selection of cases for operation, particularly as regards testing the ability of the heart to improve.

In 1908, Venus¹¹ reviewed seventeen cases from the literature, in which there was an improvement in every case.

In 1909, Lecèrne¹² reported twenty cases collected from the European literature. This series showed excellent results in seventeen, and no deaths. Mouriguand,¹³ in the same year, collected eighteen cases from the French literature, in sixteen of which the results were most successful; in two the operation failed to benefit, but there were no deaths. He expressed the belief that all cases of adherent pericarditis may be divided into two classes: (*a*) those diagnosed before death in which no adherent pericarditis was found post mortem; (*b*) those not diagnosed before death in which adherent pericarditis was found post mortem.

In 1910, Roux-Berger¹⁴ reported thirty cases from the European literature. In twenty-one of these cases the operation was successful; in seven it was a failure and in two the results were only fair; there were no deaths. He expressed the belief that before the operation was done the myocardium should be tested as advocated by Danielsen. Most authors do not agree with this view, for, while the prognosis is worse in cases in which the myocardium is affected, the operation offers the only possible hope for relief. After the release of adhesions, the myocardium has been shown to improve greatly in those cases in which the patients had had rest and digitalis previous to operation.

In 1910, Schlager¹⁵ reviewed the late results in twelve cases and expressed the belief that the immediate good results were not of long duration. He further expressed the belief that the operation was more successful in those cases that exhibited a tendency toward the development of polyserositis.

9. Kob, M.: *Jahrb. f. Kinderh.* **65**:643 (June) 1907.

10. Danielsen, W.: *Beitr. z. klin. Chir.* **54**:458, 1907.

11. Venus: *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.* **11**:401, 461, 489, 537, 1908.

12. Lecerne, P.: *Arch. d. mal. du coeur* **2**:673 (Dec.) 1909.

13. Mouriguand, C.: *Lyon chir.* **2**:781 (Dec.) 1909-1910.

14. Roux-Berger, J. L.: *Semaine méd.* **30**:423 (Sept. 7) 1910.

15. Schlager, K.: *München. med. Wchnschr.* **57**:729 (April 12) 1910.

In 1922, Klose¹⁶ reported operations on sixteen children, seven of whom died. He expressed the belief that the results would be better if adhesions were prevented by careful management of the child during the acute "rheumatic" attack. In four cases he patched the pericardial defect with fat and fascia from the thigh. He experimented on nineteen dogs and found that a flap of fat worked better than fascia, peritoneum or omentum. He further tried various chemicals to prevent reformation of adhesions, but came to the conclusion that such were useless. From the description of the operation, it would appear that he included some procedures for decortication of the heart and some for release of the pericardium from surrounding structures.

It is impossible to state how many of the cases reported by Kob, Venus, Mouriguand, Danielsen, Roux-Berger, Schlayer and Klose are duplicated, and, for that reason, they are not included in table 2. I think it is conservative to estimate that over 100 have been reported in the literature, though, for the foregoing reason, it is impossible to state the exact number.

Graham¹⁷ stated his belief that there are "literally hundreds" of these cases in which surgical relief is not being given.

For many years adhesive pericarditis has been known to pathologists, and it is interesting to note the frequency with which the different types of pericarditis have been found at necropsies.

Brooks and Lippencott¹⁸ stated:

Morgagni and Vieussens described the oblitative type of pericardium, and Corvisant in 1811 noted the significance of the bulging pericardium. Although Laennec was familiar with the lesion, he expressed his doubts as to the possibility of diagnosis. The characteristic to-and-fro rub of the acute condition was not recognized until 1824 by Collis.

Galen described the absence of the pericardium. A study of the literature on the pericardium also discloses a number of cases showing various degrees of congenital pericardial deficiencies. In an editorial in the *Journal of the American Medical Association*, Feb. 26, 1916, Keno of the Institute of Physiology, University College, London, is quoted as having proved that the pericardium was a valuable support to the heart. Keno further thought that the heart could be dilated almost to the point of rupture if it was overworked after the removal of the pericardium.

16. Klose, H.: Arch. f. klin. Chir. **119**:455 (Jan. 1) 1922.

17. Graham, E. A., in discussion on Alexander, J.; MacCleod, A. G., and Barker, P. S.: Sensibility of the Exposed Human Heart and Pericardium, Arch. Surg. **19**:1480 (Dec.) 1929.

18. Brooks, H., and Lippencott, L.: Am. J. M. Sc., 1909, vol. 138.

On the other hand, Moore,¹⁹ in 1925, collected sixty-four cases of congenital pericardial defects, and in none of these cases were there any symptoms that could be attributed to such defects. The defects are found on the left side in the vast majority of cases; in fact, in only one of the forty-two cases reviewed was the defect on the right side. Moore advanced a most interesting reason for this, based on embryology. He concluded that the existence of the pericardium is not necessary for the unimpaired function of the heart during the normal life. However, he did feel that the pericardium protects the heart from adhesions.

Grant,²⁰ in 1926, reported finding at necropsy a pericardial defect in a man 52 years of age who had worked hard during his life, but had not had any cardiac symptoms. Grant came to the conclusion that the absence of the pericardium is not a factor in connection with cardiac enlargement, and he expressed the belief that the pericardium played no part in the support of the cardiac wall.

Stone²¹ reported on 300 necropsies following pneumonia; some form of pericarditis was found in 72, or 24 per cent. Fourteen cases, or 5 per cent, showed what was classified as "fibrinplastic" pericarditis.

Hobst²² found adherent pericarditis in sixty-one cases, which was 4 per cent of all routine necropsies. It is interesting to know that in thirty of these sixty-one cases no valvular defects were found.

In 1901, McFarland²³ quoted Breitung as having collected "324 cases of pericarditis among the autopsies of the Berlin Charite, between the years 1866 and 1876." He did not give the total number of necropsies done during that period. However, 133, or 44 per cent, of these cases of pericarditis were found to be of the adhesive type.

In 1909, Fenton²⁴ reviewed 150 fatal cases of adherent pericarditis and found that in 82 death had occurred from symptoms directly dependent on the heart while in 68 death had occurred from symptoms not connected with the heart.

From these and other somewhat similar reports, it may be concluded that adherent pericarditis is not so infrequent as is generally supposed, and that the disease has been known for a long number of years.

19. Moore, R. L.: Congenital Deficiency of the Pericardium, *Arch. Surg.* **11**: 765 (Nov.) 1925.

20. Grant, R. T.: *Heart* **13**:371 (Dec. 23) 1926.

21. Stone, W. J.: Pericarditis as Complication in Pneumonia, *J. A. M. A.* **73**:254 (July 26) 1919.

22. Hobst, P. F.: *Norsk mag. f. lægevidensk.* **7**:1, 1908.

23. McFarland, Joseph: The Pathology and Pathogenesis of Pericarditis, *J. A. M. A.* **37**:1507 (Dec. 7) 1901.

24. Fenton, W. J.: *Practitioner* **81**:637 (Nov.) 1908.

It is usually regarded that the unknown cause of rheumatism, or, in the nomenclature of today, "arthritis from focal infections," is the chief etiologic factor in the production of these adhesions. However, in a brief review of some of the literature, I noted that various types of streptococci, pneumococci and staphylococci, and of tuberculosis, gonorrhea and influenza bacilli, etc., have been reported as being intimately connected with the causation of adherent pericarditis.

MacCallum²⁵ stated that bacteria are usually considered to infect the pericardium by the way of the blood stream, "since it is difficult to trace a direct extension from pleural infection and such pleurisies occur so often without pericarditis." However, Stone²¹ showed that pericarditis occurred twice as frequently following pneumonia on the left side as it did on the right. Whittemore reported a case of pneumococcus pericarditis with adhesions. He opened the pericardium (after aspiration had failed to give any aid), released adhesions, and after liberating pus, closed the incision with drainage; the patient made a rapid recovery. MacCallum²⁵ further stated that "endocardial and myocardial infection may also extend to the pericardium."

Adhesions are usually the end-results of a defensive process, and, therefore, it would be unusual to find any definite organism late in the disease. Of course, in purulent pericarditis, all the aforementioned bacteria and others have been found. Any one who is interested in purulent pericarditis will find this subject fully and most attractively discussed by Winslow and Shipley.²⁷ They collected 118 cases of suppurative pericarditis and added 10.

Darrach²⁸ instituted drainage in a case of purulent pericarditis (the type of infection not stated), and the patient remained well for two years. Then he returned with an adherent pericardium, from which he died.

There have been six cases of primary tuberculous pericarditis reported in literature since 1900. In 1904, Scagliosi²⁹ found 1 case in 1,077 necropsies; this occurred in a woman 60 years of age. In 1906, McGavean³⁰ reported a case in a woman 56 years of age. In 1925,

25. MacCallum, W. G.: Pathology, Philadelphia, W. B. Saunders Company, p. 229.

26. Footnote 26 was deleted by the author.

27. Winslow, Nathan; and Shipley, A. M.: Pericardiotomy for Pyopericardium, Arch. Surg. **15**:317 (Sept.) 1927.

28. Darrach, William, in discussion on Poole, E. H.: Ann. Surg. **73**:393 (April) 1921.

29. Scagliosi, S.: Deutsche med. Wchnschr. **30**:873 (July 9) 1904.

30. McGavean: Columbus M. J. **30**:345 (June) 1906.

Rawls³¹ reported a case. In 1928, Roubier and Langénieux³² reported 2 cases. In 1928, Alston³³ reported a case in a man of 70 years.

In 1909, Gibson³⁴ made an incision and instituted drainage in a case of tuberculosis of the pericardium with apparent success. Gibson does not know how long this patient remained well, for he disappeared from observation, but he remained free from symptoms for several years.

In 1926, Castex, Carelli and Gonzalez³⁵ injected iodized poppy seed oil 40 per cent in a case of tuberculous pericarditis to determine the presence of adhesions. They thought the procedure was of both therapeutic and diagnostic value.

In 1929, Ackermann³⁶ injected air and iodized oil into the pericardial sac of a patient with tuberculous pericarditis and reported much improvement in the patient's condition.

Thayer³⁷ reported a case of tuberculous pericarditis in which 1,200 cc. of fluid was removed by pericardial puncture. Thayer was able to follow this case for longer than three years, and after the acute process had subsided, an adhesive pericarditis without fluid developed. This case would at least suggest that an adherent pericarditis is the end-result of a tuberculous process in some cases.

Brooks and Lippencott¹⁸ stated that the same conditions that are found relative to tuberculous pericarditis pertain also to pericarditis due to syphilis.

The older writers often considered pericarditis to be due to some toxic condition, and it was in this connection that Bright reported the association of pericarditis and nephritis. It is more than likely that those cases reported by Bright were cases in which the same organism caused both the nephritis and the pericarditis.

In 1902, MacLachlan³⁸ published an extremely instructive paper on tuberculosis of the pericardium and gave a complete bibliography.

In 1901, Wells³⁹ demonstrated 10 cases of tuberculous pericarditis in 1,048 autopsies and concluded that this condition developed in about

31. Rawls, W. B.: Primary Tuberculous Pericarditis, *Am. J. M. Sc.* **169**:815 (June) 1925.

32. Roubier, C., and Langénieux, J.: *Lyon méd.* **142**:213 (Aug. 19) 1928.

33. Alston, J. M.: *Edinburgh M. J.* **35**:116 (March) 1928.

34. Gibson, C. L.: *M. Rec.* **76**:216 (Aug. 7) 1909; personal communication.

35. Castex, M. R.; Carelli, H. H., and Gonzalez, H. D.: *Bull. et mém. Soc. méd. d hôp. de Paris* **50**:217 (Feb. 12) 1926.

36. Ackermann, W.: *Am. Rev. Tuberc.* **20**:236 (Aug.) 1929.

37. Thayer, W. S.: *Bull. Johns Hopkins Hosp.* **15**:149 (May) 1904.

38. MacLachlan, W. W. G.: *New York State J. Med.* **22**:45 (Feb.) 1922.

39. Wells, H. G.: *The Pathology of Active Tuberculosis of the Pericardium*, *J. A. M. A.* **36**:1451 (May 25) 1901.

5 per cent of all cases of active tuberculosis. He further came to the conclusion that tuberculosis of the pericardium in the adherent form was a rare occurrence.

Norris,⁴⁰ on the other hand, after a somewhat similar study, concluded that tuberculosis accounted for a large number of those adherent lesions. He further considered that these adhesions represented, in many instances, healed tuberculous lesions that could not be demonstrated by histologic studies, but by inference.

MacLachlan³⁸ stated, "It seems rather strange that calcification, a cardinal sign of healed tuberculosis, when it occurs in the pericardium, very rarely means this disease." It is interesting to note that the report by Cutler and Sosman,⁴¹ in which they reviewed two cases of calcification of the pericardium, showed that one of these cases was definitely tuberculous in origin, while in the other one, they concluded that the "process must represent the late stage of healing of the infection." Unfortunately, full clinical data could not be obtained in this case.

In 1927, Taylor⁴² reported a case in which the "influenza" bacillus was isolated from the pericardial fluid in pure culture.

In 1905, Huber⁴³ reported a case of acute gonorrheal pericarditis, and in 1909, Bubis⁴⁴ also reported a case of this type.

The pericardium and its adhesions do not differ from other structures in the late development of calcareous deposits and infiltrations. The literature shows ninety-six cases reported.

In 1923, Case⁴⁵ reported ninety cases from the literature, to which he added one. In his report he gives a list of all the references. Since this time the following five cases have been reported: Schlesinger,⁴⁶ one case in 1926; Kirschner and Matthes,⁴⁷ one case in 1926; Arnesen,⁴⁸ one case in 1927, and Starck,⁴⁹ two cases in 1928. In these cases of calcareous pericarditis there have been four attempts to remove a part of the stonelike pericardium. The results have not been entirely successful.

40. Norris: Univ. Pennsylvania M. Bull., 1904, vol. 17.

41. Cutler, E. C., and Sosman, M. C.: Am. J. Roentgenol. **12**:312 (Oct.) 1924.

42. Taylor, Ruth E.: Influenzal Pericarditis, J. A. M. A. **89**:347 (July 30) 1927.

43. Huber, F.: Arch. Pediat. **21**:919, 1904.

44. Bubis, J. L.: Cleveland M. J., December, 1909.

45. Case, James T.: Pericarditis Calculosa, J. A. M. A. **80**:236 (Jan. 27) 1923.

46. Schlesinger, H.: Med. Klin. **22**:11 (Jan. 2) 1926.

47. Kirschner, M., and Matthes, M.: Deutsche med. Wchnschr. **52**:221 (Feb. 5) 1926.

48. Arnesen, J.: Norsk mag. f. laegevidensk. **88**:688 (Aug.) 1927.

49. Starck, H.: Med. Klin. **24**:1735 (Nov. 9) 1928.

In 1923, Lilienthal⁵⁰ reported a case of calcified pericardium in which he attempted to remove the stonelike structure. Before completing the operation, he injured the auricle and was, therefore, unable to continue. The patient slowly recovered with a persistent sinus tract. Lilienthal further stated, "If I were to operate in another case, I should begin removal of the calcified pericardium over the cardiac apex gradually working up toward the thinner and more dangerous region of the auricle." This patient (personal communication from Dr. Lilienthal) lived over a year. She did not die in the hospital, and no post-mortem examination was allowed.

In 1923, Cutler and Sosman⁴¹ removed a portion of a calcified pericardium. This was found to be so difficult as to require the use of rongeurs. They found the calcification also involving the myocardium. The patient died in twenty-four hours. These authors also reported two other cases in which on autopsy the calcification was found to extend not only to the myocardium, but it also involved the diaphragm. They mentioned another case in which roentgenoscopic examination showed "calcification in the region of the mitral valve." This case gave no "evidence that the calcification has any particular significance."

All the authors who have discussed calcification of the pericardium, since the advent of the x-rays, have stressed the importance of utilizing this agent in the diagnosis of this condition.

With the heart embarrassed by adhesions, it is not surprising to find hepatic changes and serous cavities filled with fluid. In these cases the liver is usually three or four times its normal size, and the condition is sometimes referred to as Pick's pericardiac pseudocirrhosis. Much has been written on the pathologic changes in the liver and other morbid processes associated with chronic mediastinopericarditis and adherent pericarditis. Any one particularly interested in such studies is referred to textbooks by Pick,⁵¹ Rolleston,⁵² Hirschfelder,⁵³ and Smith,⁵⁴ all of whom have written full descriptions of the pathologic changes in the various organs, which are due to the cardiac failure dependent on pericardial adhesions.

50. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1926, vol. 2.

51. Pick, F.: *Ztschr. f. klin. Med.* **29**:385, 1896.

52. Rolleston: Diseases of the Liver, Gallbladder and Bile Ducts, New York, The Macmillan Company, 1912.

53. Hirschfelder, A. D.: Diseases of the Heart and Aorta, ed. 2, Philadelphia, J. B. Lippincott & Company, 1913.

54. Smith, E. S.: *M. Clin. North America* **4**:835 (Nov.) 1920.

It is interesting to recall that Rohde⁵⁵ produced experimentally a stenosis of the vena cava at the site between the pericardium and the diaphragm, which gave many of the results of an adherent pericardium, such as enlarged liver, ascites and polyserositis.

Before the association between the pericardial adhesions and the enlarged liver was as well understood as it is today, it was thought that Talma's operation on the liver might be of value. Clemens⁵⁶ thought that he noticed temporary improvement in the one case in which he did this operation. However, Smith⁵⁴ reported a case of chronic mediastinopericarditis in which Talma's operation had been done without any benefit. These two cases serve to show how it is possible for symptoms due to enlarged liver to mislead one unless the possibility of an adherent pericarditis is kept in mind.

Bittrolff⁵⁷ did Talma's operation on a patient on whom he had previously performed the Delorme operation with complete relief from the abdominal symptoms.

It is essential to be able to differentiate between the symptoms due to an enlarged liver resulting from myocardial and valvular cardiac disorders and those symptoms due to an enlarged liver resulting from pericardial adhesions. Some authors stated that when an enlarged liver is found and this enlargement is due to the heart and no valvular disease is located, then the symptoms must be due to adherent pericarditis.

AIDS TO DIAGNOSIS

When the morbid anatomy is so well understood and the operative relief so thoroughly described, there must be some reasons why surgical aid is not sought more often. I think these reasons may be found in the uncertainty and difficulty of diagnosis, as well as in the general lack of appreciation of beneficial results of certain operative procedures which have not received the credit they deserve.

The making of the diagnosis of pericardial adhesions does not differ from many other diseases in that carefully taken and honestly analyzed history is of prime importance. For example, in examining a patient who has had some serious infection in youth, such as is usually called "rheumatism," who develops an enlarged liver, is easily exhausted and presents no cardiac murmurs, the diagnosis of adherent pericardium should be given serious consideration. It would be of great aid to remember that any infection in youth that continues longer

55. Rohde, C : *Deutsche Ztschr. f. Chir.* **203-204**:18, 1927.

56. Clemens, P.: *München. med. Wchnschr.* **1**:936, 1903.

57. Bittrolff, R.: *München. med. Wchnschr.* **71**:517, 1924.

than is usual and is unexplained by some more plausible reason than "lowered resistance" might have been a pericarditis, which later in life produced the symptoms of an adherent pericarditis.

In 1929, Dr. Evelyn Holt⁵⁸ of the cardiac clinic of New York Hospital stated that "in 1898 Sir John Broadbent said that the key to the solution of the problem of adherent pericardium seemed to lie in the investigation of cases of pericarditis which could be kept under observation while going on to the formation of adhesions." With this in view, she studied fifty-one cases of chronic adhesive pericarditis in children. Only six of these patients are leading a reasonably normal life. Twenty-one died within four years, and sixteen are apparently growing worse. She was unable to trace eight. It is probable that a fairly large percentage of the six persons who are now leading a "reasonably normal life" will later develop some type of adhesive pericarditis, and unless a careful history is taken, this possibility will be overlooked.

The symptoms are usually insidious in origin and develop slowly, sometimes over a period of years. Frequently the patient complains of pain in the region of the heart, and this is often exaggerated on exertion. If the disease is allowed to progress, many other symptoms are added as the various other organs become involved.

Musser and Herrmann⁵⁹ reviewed 1,720 necropsies, 305 of which showed various types of pericarditis. From a careful analysis of the clinical history in 68 of the 305 cases, they felt that death was due directly to pericardial involvement. They also produced adhesive pericarditis in dogs by injecting permutit into the pericardium and then observing the dogs for "any one or more conditions that would invariably indicate pericardial disease." Their conclusions are as follows:

1. It is generally agreed that adhesive pericarditis is rarely diagnosed ante mortem.
2. There are no pathogenic signs found in all cases.
3. The diagnosis depends in part on the history, to which is added a thorough survey of the physical signs and the electrocardiographic and roentgenologic examinations.
4. Experimental pericarditis has not yielded any positive information.

In nearly one half of the cases of adhesive pericarditis there are also found either myocardial changes or cardiac valvular disease. Not

58. Holt, Evelyn: *Am. J. M. Sc.* **178**:615 (Nov.) 1929.

59. Musser, J. S., and Herrmann, G. H.: *Chronic Pericarditis*, *J. A. M. A.* **87**:459 (Aug. 4) 1926.

infrequently is there a combination of all three of these complications. Occasionally, the patient's attention is first attracted by the fulness and firmness of the abdomen and an enlarged liver. It is possible, at this time, that the patient has no edema of the legs. An examination of the urine is negative, except possibly for the presence of a little bile, and the heart sounds disclose no murmurs. This picture should make every physician suspicious of pericardial adhesions.

Beck and Griswold⁶⁰ actually "champion diagnostic pericardiotomy in selected cases of circulatory failure of obscure cause."

It will be of aid to remember that adherent pericarditis is a progressive disease, and therefore the symptoms will vary with the type, extent and location of the adhesions. At the apex of the heart, there is frequently a systolic tug or retraction with a diastolic shock or rebound. It is of much importance to note that the apex beat does not change its position when the patient is turned from side to side. This is even true if the patient is allowed to stand. Regelsberger⁶¹ stated that in doubtful cases this diastolic bulging and systolic retraction is sufficient to make the diagnosis. Of course, this sign is not present when there is a leather-like shell of thickened pericardium surrounding the heart, thus preventing any cardiac impulse from reaching the thoracic wall. If the adhesions are due to a mediastinopericarditis which has extended to the back, Broadbent's⁶² sign is frequently present. This sign is a "visible retraction, synchronous with the cardiac systole of the left back in the region of the eleventh and twelfth ribs."

Thayer³⁷ "found the third heart sound and the corresponding protodiastolic shock and wave very distinct in adherent pericardium."

Pulsus paradoxus (Kussmaul's sign) occurs, i. e., the pulse intermits during inspiration, most often in mediastinopericarditis. This may occur in healthy subjects.

There may be peculiar movements in the great vessels of the neck as if the blood current was hindered in its flow; it gives one the impression that the ventricle is making an effort to drive the blood into those vessels but is prevented from doing so by adhesions. Of course, these arterial movements may be modified by valvular lesions. In recent years this has been shown to be caused by other conditions. Curschmann⁶³ suggested that this condition might be due to pressure of the scalenus minimus muscle on the subclavian artery during inspiration.

60. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome, *Arch. Surg.* **21**:1064 (Dec.) 1930.

61. Regelsberger, H.: *Deutsches Arch. f. klin. Med.* **147**:129 (May) 1925.

62. Broadbent, William H.: *Lancet* **2**:200, 1895.

63. Curschmann, H.: *Med. Klin.* **18**:1521 (Nov. 26) 1922.

In referring to cases "when the heart is throttled by a contracting pericardium," Churchill stated that "the most striking single characteristic of the picture is marked stasis with a small heart."

The cervical veins are frequently dilated in cases of pericardial adhesion, and should a tricuspid regurgitation develop, they pulsate. A sudden collapse of the veins of the neck during ventricular systole is often present (Friedrich's sign), and when associated with a systolic retraction of the intercostal spaces, is a very valuable sign.

Bigger⁶⁴ and his associates, Drs. Burwell and Strayborn, estimated "the venous pressure and blood flow determinations" in one of his two cases. They expected to repeat these observations after the operation, but unfortunately the patient died. Beck and Griswold⁶⁵ estimated the venous pressure in their case and found that it fell rapidly on releasing the heart from its constricting shell. They expressed the belief that venous pressure is the most reliable index of a contracting and restraining pericardium.

If the two walls of the pericardium rub at any point against each other, friction sounds can be heard. De Teyssier⁶⁵ reported one case in which there was a rather small collection of pericardial fluid that produced such friction sounds; this observation was confirmed at autopsy. The case was one of tuberculous pericarditis.

Richter⁶⁶ also reported one case of adherent pericardium in which he heard friction sounds. Autopsy disclosed old blood clots in the loose connective tissue of the pericardial adhesions, to which he attributed these friction sounds.

Another interesting sign was reported by Riess,⁶⁷ namely, loud and metallic heart sounds heard over the stomach. Riess attributed these sounds to adherence of the pericardium to the diaphragm.

Apparently, there is no sign in the diagnosis of adherent pericardium concerning which there has not been contradictory reports. The roentgenogram and the electrocardiogram are not exceptions. This discrepancy is not hard to understand, for no one person or clinic has had a sufficient number of cases to formulate any definite observations. There has been a sufficient number of cases, however, for most diagnosticians to feel that by the aid of these two agents the most reliable information available may be obtained.

In 1923, Lukin⁶⁸ reported a fluoroscopic sign of a partially adherent pericardium, which he described as a "rhythmic tug of a part of the

64. Bigger, I. A.: Personal communication, Nov. 14, 1930.

65. de Teyssier, J.: *Lyon méd.* **127**:499 (Nov.) 1915.

66. Richter, E.: *Berl. klin. Wchnschr.* **45**:821 (April 27) 1908.

67. Riess, L., quoted by Hirschfelder: *Diseases of Heart and Aorta*. Philadelphia, J. B. Lippincott Company.

68. Lukin, N.: *A Fluoroscopic Sign of a Partially Adherent Pericardium*, *J. A. M. A.* **81**:1952 (Dec. 18) 1923.

left dome of the diaphragm near its centre with each systole of the heart when the diaphragm was fixed in an inspiratory frame." This shadow disappears entirely in forced inspiration, the heart being separated from the diaphragm by a clear space, which corresponds to the base of the left lung, and the lower edge of which is outlined for the greater part of its length against the clearness of the pulmonary tissues. The rhythmic tug of a part of the diaphragm with each systole of the heart is distinctly visible in that clear space when the phrenum is fixed in inspiration because the visceral pericardium is adherent to the parietal pericardium, even though in a small degree, and exerts a pull on it and through its insertion on the diaphragm with each cardiac contraction.

The patient in whom this sign was observed had recovered from a serofibrinous pericarditis nine months previously. Lukin also observed the same sign in another patient who had had a "rheumatic endopericarditis" two years previously.

In 1924, Holmes⁶⁹ published his roentgen observations in sixty cases of pericarditis of various types. He stated:

In the normal heart, it is usually possible, under the fluoroscopic observation, to differentiate the pulsations of the auricle from those of the ventricle. In the presence of pericarditis, and particularly if fluid is present, the pulsation becomes diffuse over the entire cardiac area, and it is impossible to distinguish the auricular beat from that of the ventricle. While the making of this observation requires considerable experience to be accurate, it apparently does not occur in any other cardiac condition, and when found must be considered as almost pathognomonic. This sign is especially valuable as it is present in adhesive pericarditis, as well as pericarditis with effusion.

We have found that the obliteration or change in the shape of the cardio-hepatic angle (Retch's sign) is more likely to occur in pericarditis with adhesions than with fluid, and that it is not a reliable finding in any case. This observation has been confirmed by other writers. . . . Other findings, such as retraction of the diaphragm with the heart beat, and fixation of the heart within the chest as shown by failure to be displaced when the patient is turned from side to side, are subject to so much error in observation by the roentgen ray that we have found them of little value.

Holmes⁶⁹ concluded by saying:

From this data it would seem that the roentgen-ray is of considerable value in making a positive diagnosis of pericarditis, and that a negative roentgen-ray finding make a negative diagnosis probable.

In the discussion following his paper, Holmes concluded:

I should like to mention the value of the respiratory study of the heart during adhesive pericarditis. In the lateral view, particularly if the mediastinum is

69. Holmes, G. W.: Some Observations on the Use of Roentgen Rays in the Diagnosis of Pericarditis, *J. A. M. A.* 83:1745 (Nov. 29) 1924.

involved, the heart may rise with the chest wall instead of dropping with the diaphragm during forced breathing. This is a very definite and easily interpreted sign.

Chandlee and Burrill-Holmes⁷⁰ reviewed 100 cases of disease of the heart and of the great vessels in the cardiac clinics of the Philadelphia General Hospital, and I quote the following from their report:

In chronic adhesive pericarditis, the lack of mobility of the apex is visualized on fluoroscopic examination and the heart does not show the normal shadow separating the shadow of the diaphragm on inspiration. Films occasionally show deformity of the pleuropericardial diaphragmatic shadows, and it is probably because of these adhesions that many pleuro-pericardial friction sounds are heard clinically. . . . The fluoroscopic study helps explain the low and fixed position of the apex seen particularly in mitral stenosis accompanied by pericarditis.

If the heart is surrounded by a leather-like shell, as it was in the case in which I operated, only slight, if any, cardiac movement can be seen with the fluoroscope. Of course, if the pericardium has deposits of calcium, these can be seen with the fluoroscope and shown on the plate, as has been mentioned previously.

There is normally a change in the form of the electrocardiogram on shifting the patient to the right or to the left side. This is due to rotation of the heart about a longitudinal axis. The change in the height and conformity of the QRS wave in the different leads is the most noticeable, though all the waves are affected to a certain degree. All three leads are affected but usually only leads I and III show marked variation. Dieuaide⁷¹ has made application of this phenomenon in the diagnosis of an adherent pericardium. In curves on cases of chronic adhesive pericardial mediastinitis this normal change, shift of the electrical axis, is absent and is believed diagnostic of the condition.

In electrocardiograms of abnormalities on patients presenting suggestive signs of adhesive pericarditis other changes may be noted. These are abnormalities of the T wave, low voltage, notching and slurring of the QRS complex. However, the only change that seems directly due to adhesions is fixation of the electrical axis.

Articles concerning electrocardiographic studies by Porte and Pardee,⁷² Becke, Johnson and Harris,⁷³ Carter and Dieuaide,⁷⁴ and Holt⁷⁵ will be found of interest and aid.

70. Chandlee, E. J., and Burrill-Holmes, E.: *Am. J. M. Sc.* **178**:364 (Sept.) 1929.

71. Dieuaide, F. R.: *Electrocardiograms as Aid in Diagnosis of Adhesive Pericardial Mediastinitis*, *Arch. Int. Med.* **35**:362 (March) 1925.

72. Porte, D., and Pardee, H. E. B.: *Am. Heart J.* **4**:584 (June) 1929.

73. Becke, W. G.; Johnson, S., and Harris, H. S.: *Am. Heart J.* **2**:302 (Feb.) 1927.

74. Carter, E. P., and Dieuaide, F. R.: *Bull. Johns Hopkins Hosp.* **32**:219 (July) 1921.

AIDS TO OPERATION

It is not only essential to make the correct diagnosis of adherent pericardium, but also highly important to determine as accurately as possible the extent and the location of the adhesions before proceeding to undertake any type of operation. Manifestly, if the adhesions are between the pericardium and the thoracic wall, the removal of the pericardium is both dangerous and unnecessary. On the other hand, if the heart is surrounded by a leather-like shell, the removal of the ribs will not give the required relief.

The following is a suggestion, which, as far as I can find, has not been used to assist in the release of pericardial adhesions as a supplementary aid to the Brauer operation. However, since writing the foregoing paragraph, I have obtained the following quotation from Sauerbruch's⁷⁵ textbook on surgery of the thoracic organs after a search of the German medical journals had failed to reveal any such reference:

In mediastino pericarditis and tuberculous adhesions which exist between heart and lung on one hand and the diaphragm on the other, phrenicotomy relieves the tension and pulling and frees the patient from disagreeable discomfort. It therefore also serves as an adjunct for the operative loosening of the heart (cardiolysis). One has also thought of combating singultus by elimination of the phrenic nerve.

It is reasonable to presume that the removal of the bony resistance in the chest to the cardiac impulses gives relief only in those cases in which the adhesions are between the pericardium and the surface from which the ribs and cartilages have been removed. There are cases in which the adhesions exist between the pericardium and the thoracic wall, and also between the pericardium and the diaphragm. It is in such cases as these that I believe the removal of a segment of the left phrenic nerve will be of value.

While I have had no case of chronic mediastinopericarditis in which I could try this, I have recently had five cases in which I did avulsion of the left phrenic nerve for pulmonary tuberculosis. In each one of these cases, the heart shadow was drawn somewhat further than normal to the left and adherent to the diaphragm, e.g., the cardiohepatic angle was obliterated (Rotch's sign) by the tuberculous process. After the avulsion of the left phrenic nerve, the heart shadow returned markedly to its normal position. All these patients had been in bed for months before operation, yet, after the avulsion of the left phrenic nerve, there were a decided increase in the blood pressure and a decrease in the pulse rate. Apparently, the cases of pulmonary tuberculosis in which a phrenic avulsion has been done on the left side have improved

75. Sauerbruch, E.: *Die Chirurgie der Brustorgane*, Berlin, Julius Springer 1925, vol. 2, p. 694.

more satisfactorily than those in which the right phrenic nerve had been avulsed. However, there are so many other factors to be considered, that it would be impossible to draw any fair conclusions from a comparison of the two sides.

Cole reported a case done by Johns in which an avulsion of the left phrenic nerve had produced marked benefit of symptoms. Further relief was obtained by removal of the cartilages of the third, fourth and fifth ribs.

In a personal communication, Dr. John Alexander stated:

From time to time I have casually wondered whether the results following phrenicectomy for tuberculosis should be better upon the right or the left side, and because of the press of other things, my curiosity has stopped there. I do seem to remember that one or two men in writing (I do not know the references) have mentioned a possible swinging of the heart and mediastinal organs toward the right side after a left phrenicectomy, and it is quite reasonable to suppose that any cardiac disability due to traction of mediastino-pericardial adhesions might thereby be relieved. I do not know that anyone has ever suggested the possibility of left phrenicectomy being a useful complementary operation together with a Brauer cardiolysis, nor do I recall anyone's ever having compared the results as between right and left-sided operations. In my clinic there have now been three hundred or more phrenicectomies and my casual impression is that the good, medium and poor results have been approximately equally divided between both sides. I do know that striking results have occurred on both sides.

Smith⁵⁴ stated:

In one case of mediastinopericarditis we were fortunate enough to obtain fluoroscopically definite evidence of adherent pericardium, in our being able to see distinctly a tugging upward of the diaphragm with each cardiac systole. . . . We have not met with any allusion to this sign of systolic tugging on the diaphragm in the literature. . . . It was very apparent, during deep inspiration, that the left diaphragm was more or less fixed toward the apical shadow of the heart, being pulled upward or tugged in synchronism with each heart throb. . . . These observations were observed to be more pronounced following rotation of the patient in the semi-oblique position, while the apex shadow was in close proximity to the fluoroscopic screen.

This (tugging) was accentuated during deep inspiration, forcibly pulling the left side of the diaphragm for a distance of at least 3 cm. with each pulsation of the heart.

Hobst²² did autopsies in two cases in which the Brauer operation had been done. There had been great relief from symptoms in one case for five years, and, in the other, for four. Then the enlarged liver, ascites, etc., returned, and after frequent tapping of the abdomen, both patients died. Necropsies showed dense adhesions between the pericardium at the apex and the diaphragm with only slight adhesions between the front of the chest from which the cartilage had been removed. The condition of the pericardium was not such as would have been benefited by the Delorme type of operation.

In 1918, Trémolières and Caussade⁷⁶ reported twenty cases of a condition to which they give the name of "phreno-pericarditis." The symptoms suggested angina pectoris, and the x-ray plates showed the heart and diaphragm soldered together. It is possible that a phrenic avulsion may have been of some aid in these cases.

It is also interesting to note that Schmieden,⁷⁷ in 1923, warned against injury to the phrenic nerve while doing the decortication of the heart. Since that time many phrenic nerves have been avulsed during the treatment of pulmonary tuberculosis and apparently without any serious consequences. In 1926, Schmieden⁷⁸ stated that injury to the left phrenic nerve was not harmful.

It should be remembered that operations on the pericardium can be done in progressive stages with far greater safety than the previous attempts at completing the operation at one time. In chronic mediastino-pericarditis with the apex of the heart pulling against the bony chest, the so-called Brauer operation should be done first. If this does not give sufficient relief, and the roentgenogram shows combating adhesions between the pericardium and the diaphragm, then the avulsion of the left phrenic nerve should be seriously considered. It is possible for the diaphragm to be so fixed by scar tissue that the paralysis of the muscles would have but little chance of relaxation. However, it is highly improbable that the diaphragm will ever be so extensively infiltrated with fibrous tissue that some muscle tissue will not remain free from such invasion. If any muscle is left not involved then a paralysis would tend toward some relaxation. It is also reasonable to presume that there must be occasions in those cases in which the pericardium is adherent to the diaphragm, when the cardiac tug is in an opposite direction to that of the diaphragm, either in ascent or descent. In other words, if these two organs do not synchronize, then there follows a conflict when they are bound together by adhesions. Paralysis of the diaphragm should certainly give control to cardiac impulses.

Welles,⁷⁹ reported the results on the pulmonary conditions in 271 cases in which phrenic avulsion had been done. He concluded that the lack of motion of the diaphragm before operation, as observed by the fluoroscope, is not a contraindication to phrenic avulsions for the diaphragm becomes elevated in spite of having been apparently fixed before operation.

Of course, neither of these procedures would be of aid in releasing the heart from a leather-like shell, but, in such conditions, the pericar-

76. Trémolières, F., and Caussade, L.: *Presse méd.* **26**:169 (April 4) 1918.

77. Schmieden, V.: *Klin. Wchnschr.* **2**:5 (Jan. 1) 1923.

78. Schmieden, V.: *Surg., Gynec. & Obst.* **43**:89, 1926.

79. Welles, E. S.: Phrenicectomy in Three Hundred Cases of Pulmonary Tuberculosis. *Arch. Surg.* **19**:1169 (Dec.) 1929.

dium can be approached in stages, if the patient's condition either requires or permits a graded and cautious delivery. In other words, each patient is necessarily "a law unto itself," and the surgical procedures will have to be made to fit not only the type and extent of the pericardial adhesions, but also the condition of the patient.

In operations on the pericardium, the choice of the anesthetic is of prime importance, but even more important than that is the selection of the proper anesthetist. Personally, I prefer ethylene administered by the closed method in thoracic surgery, because it has the following advantages:

(a) It does away largely with psychic shock of a local anesthetic.

(b) In case the pleura is opened, the opening can be closed and the lung expanded from the rebreathing bag.

(c) With nitrous oxide, the patient with a pulmonary condition becomes more cyanotic.

(d) Ethylene does not apparently tend to "light up" old pulmonary lesions as other anesthetics do.

(e) "Avertin" keeps the patient asleep for several hours after the completion of the operation and thus allows aspiration into the right lung from the compressed left lung.

In the Brauer operation, the incision is started over the third rib about 5 inches (12.7 cm.) from the sternum and carried over the rib to the midline of the sternum. The incision goes down the midline of the sternum to its juncture with the seventh rib. From this point the incision is continued outward over the seventh rib to a point about 6 inches (15.24 cm.) from the sternum. The skin, fat and pectoralis major muscle are dissected up in one flap and the same reflected outward so as to freely expose the cartilages of the third, fourth, fifth and sixth ribs. These cartilages are removed so as to leave the bed of the perichondrium. It is usually best to remove about 1 inch (2.5 cm.) of the fourth, fifth and sixth rib, but leaving behind the posterior periosteum. If the pleura is accidentally opened, a purse string suture of chromic catgut is placed around that opening, the collapsed lung is expanded by the anesthetist, and when the lung has returned to its full capacity, the purse string suture is tightened. If after the removal of these bony and cartilaginous tissues there still remains any point at which the cardiac tug meets with resistance, then that resisting tissue is removed. Frequently this is found to be the sternum, and the same can be removed safely and easily with rongeur forceps.

Shipley⁸⁰ recently performed a Brauer type of operation for the relief of pain due to an aneurysm of the aorta. His patient had immediate relief, but this relief is most likely only temporary.

80. Shipley, A. M.: Personal communication.

In 1925, Hughson⁸¹ resected the fourth, fifth and sixth costal cartilages in a case of Hodgkin's disease. The mediastinal glands were so greatly enlarged as to give symptoms of cardiac pressure. During the operation, the patient's pulse went as high as 180 per minute, but on releasing the pressure by freeing the adhesions and "boning the chest wall" the pulse became very much slower, and the patient's general condition improved. The patient died from the Hodgkin's disease without developing any further symptoms of cardiac pressure.

In 1930, Whittemore⁸² removed the cartilages, opened the pericardium and released some adhesions in a case of extensive cardiac enlargement due to valvular disease. This patient showed improvement for ten days, and then died. No autopsy was obtained. Also in 1930 Alexander,⁸³ lifted up the sternum and the cartilages in a case of depressed fracture, with great improvement in the cardiac symptoms. He reported one case in which the Brauer type of operation gave much relief from the anginoid pain.

In 1901, Preble⁸⁴ reported that aneurysm of the aorta is associated with 26 per cent of all cases of pericarditis, which he further stated to be "a very high figure when one recalls the comparative infrequency of aneurysm."

In 1929, Graham⁸⁵ did a Brauer type of operation in two cases in which the hearts were so large that they could not "help being embarrassed by confinement within a bony chest wall." Graham stated that the results in both of these cases were excellent. Graham further stated this procedure was first advocated by Alexander Morison of Edinburgh, in 1907.

By leaving the perichondrium and the periosteum, the chances of regeneration of the cartilage and the bone are good, and when this has occurred resistance by the thoracic wall again develops. For this reason, some surgeons have attempted to remove the perichondrium and the periosteum, along with the cartilages and ribs, and by so doing, have greatly increased the chances of perforating the pleura.

In 1927, Head⁸⁶ completed some experimental work on dogs which gives great promise of being of much assistance in providing the regeneration of ribs. In these experiments he used: (1) the "silver

81. Hughson, Walter: Personal communication, Nov. 28, 1930.

82. Whittemore, Wyman: Exploration of the Pericardium and Decompression of the Heart, *Arch. Surg.* **21**:1059 (Dec.) 1930.

83. Alexander, John, in discussion on Beck and Griswold: *Arch. Surg.* **21**:1112 (Dec.) 1930.

84. Preble, Robert B.: Etiology of Pericarditis, *J. A. M. A.* **37**:1510 (Dec. 7) 1901.

85. Graham, E. A.: *Ann. Surg.* **90**:817 (Nov.) 1929.

86. Head, J. R.: Prevention of Regeneration of the Rib, *Arch. Surg.* **14**:1909 (June) 1927.

nitrate stick"; (2) 50 per cent solution of silver nitrate; (3) concentrated solution of chromic acid, and (4) Zenker's fluid. He demonstrated that anything that would kill the superficial cambium layer of cells would prevent regeneration of ribs. Of the four agents, he found Zenker's solution the most satisfactory. It is more than possible that if a latent infection is present, Zenker's solution might also help to control the same. While I have had no opportunity to try Zenker's solution in doing the cardiolysis operation, I have had excellent results with it in preventing the regeneration of ribs in operations for pulmonary tuberculosis.

For the avulsion of the phrenic nerve, only procaine hydrochloride is used. After locating the nerve, the patient is placed under the fluoroscope, and the diaphragm on both sides observed. If the phrenic nerve has been correctly located, pinching the same with a clamp will allow the diaphragm to rise several inches. When the patient coughs, the affected side does not synchronize with the opposite half of the diaphragm. After being certain that the phrenic nerve is correctly and definitely located, it can be removed. The Alexander clamp is of much assistance in twisting out this nerve, for the flange prevents the nerve from falling off at the tip.

If the x-ray plate and the fluoroscope demonstrated adhesions between the pericardium and the vertebra, no way has as yet been devised for the liberation of such adhesions.

If it has been determined by the x-rays that the heart is surrounded by a thick nonresisting shell, these two operative procedures will be of no aid in the relief of symptoms. The removal of the thoracic wall (Brauer's operation) can be utilized as the primary step in the operation for the decortification of the heart (Delorme). In fact, if any accident occurs, such as the unexpected finding of pus or the puncture of the pleura, the operation can be halted. After the improvement in the patient's condition the next stage in the operative procedure can be undertaken. Following the removal of the cartilages, it is advantageous to tie the internal mammary vessels at the second interspace close to the sternum.

In the approach to the pericardium, it is well to recall the anatomy of the interpleural space: "the uncovered pericardial triangle of Voinitch-Sianojentsky, or the triangle of safety" (Matas). It is some comfort to recall also that the two pleural reflections surrounding this "triangle of safety" are apt to be adherent to each other due to the previous infection, and that injury to the pleura will not necessarily mean collapse of the lung. Frequently the pleura can be wiped away, as suggested by Cutler, by the use of wet cotton pledgets on the end of a clamp. As a rule, however, those adhesions require sharp and careful dissection.

Every reasonable effort should be made to obtain full exposure of the pericardium before the same is incised. Frequently, it is wise to remove a part of the sternum so that the pericardium on the right side of the heart can be removed, if indicated.

Apparently the section of the sternum as advocated by Duval-Barastý produces too great a shock to be employed as the incision of choice. In 1930, Beck and Griswold⁸⁰ suggested the possibility of an incision in the skin through the center of the sternum with two cross arms at each end of this incision. The flaps are then dissected out on each side, and the cartilages removed from both sides of the sternum. This method would allow the sternum to remain undisturbed, and give access to both sides of the pericardium.

Lilienthal⁸⁰ used the Duval-Barastý midsternal incision in one of his cases and obtained excellent exposure. He further called attention to the fact that this exposure left the wall of the chest intact.

Churchill¹ expressed the belief that a flexible precordial area was of advantage as the heart is apt to become adherent to the thoracic wall, and it would be better to have the heart fixed to a pliable structure than to a firm one.

Schmieden and Fischer⁸⁷ suggested a transpleural route through the pleural cavity when before operation it has been determined necessary to release the scar from the left side of the heart.

In 1910, Heitler⁸⁸ demonstrated in experiments on dogs under ether that incision of the pericardium showed great disturbance of the pulse unless the pericardium was first cocainized with a 10 per cent solution. In 1912, D'Agata⁸⁹ confirmed the observations of Heitler but showed that a much weaker solution of cocaine was equally as efficacious.

Harrigan⁹⁰ reported a case of suppurative pericarditis in which the heart stopped beating just as soon as an incision was made in the pericardium with the liberation of about 1,000 cc. of pus. He concluded that the behavior of the heart was due to the incision of the pericardium, but apparently did not seem to consider the possibility of the effects of the sudden liberation of such a great quantity of fluid. Harrigan concluded his report with this passage: "If this relationship between pericardium and myocardium be definitely established, then it will be necessary to revise the present technique of cardiac surgery."

On the other hand, Capps,⁹¹ in 1927, demonstrated that there was no sensation in the pericardium unless the pleura was involved.

87. Schmieden, V., and Fischer, H.: *Ergebn. d. Chir. u. Orthop.* **19**:98, 1926.

88. Heitler, M.: *Med. Klin.* **6**:1562 (June 19) 1910.

89. D'Agata, G.: *Arch. f. klin. Chir.* **98**:460 (July 8) 1912.

90. Harrigan, A. H.: *Ann. Surg.* **57**:367 (March) 1913.

91. Capps, J. A.: *Pericardial Pain*, *Arch. Int. Med.* **40**:715 (Nov.) 1927.

Alexander, Macleod and Barker ⁹² had an excellent opportunity to observe cardiac sensibility in a patient with purulent pericarditis. They concluded:

When pressure was applied forward against the anterior pericardium and thoracic wall, there was some local and referred pain. . . . Pain was also produced by sweeping the finger around the pericardial cavity, by pinching, pricking and scratching the inner surface of the pericardium. Heat and cold were not identified. . . . Our observations do not justify conclusions as to the nerve paths concerned in the sensations produced.

As the sensibility of the pericardium is not definitely established, it is safer, if possible and practical, to inject into the same procaine hydrochloride. The pericardium is opened just over the left ventricle. If the right ventricle is freed first, a fatal tricuspid insufficiency may develop. This would, perhaps, be due to the fact that the ventricle accustomed to its encasement by the leather-like shell, would become acutely dilated when this restraint is removed. It is always well, however, when these adhesions are found, to cut the same close to the pericardium, and as far away as is possible from the coronary vessels. Reference has already been made to the finding of deposits of calcium and infiltrations.

Most authors, who have released hearts from such leather-like shell, speak of the manner in which the "heart leaps to freedom" or some similar expression. Certainly, in the one case in which I operated, the heart was apparently far more anxious to escape than I was to have it do so. The pericardium should be removed in strips about 2 cm. in width and great care always exercised not to injure the myocardium. A piece of pericardium about 7 by 12 cm. should be removed—at least enough to be certain the heart is free. It is important also to be certain that the adherent pericardium is removed from around the great vessels. This can be best done by removing V-shaped pieces of pericardium with the apex of the V toward the vessels. It is wise to be certain there are no pockets of pus or adhesions on the posterior wall of the heart. This can be ascertained by gently passing the fingers around back of the heart. No attempt should be made to free any adhesion with the finger, but exposure should be obtained and the adhesion cut. Ochsner ⁹³ assisted Schmieden in three cases of decortication of the heart and was much impressed with the marked fibrosis that existed not only of the pericardium but also of the myocardium and the epicardium.

Beck and Griswold ⁹⁰ produced Pick's syndrome by creating adherent pericarditis with the introduction of surgical solution of chlorinated

92. Alexander, J.; Macleod, A. G., and Barker, P. S.: Sensibility of the Exposed Human Heart and Pericardium, *Arch. Surg.* **19**:1470 (Dec.) 1929.

93. Ochsner, Alton, in discussion on Alexander; Macleod, and Barker: *Arch. Surg.* **19**:1481 (Dec.) 1929.

soda (Dakin's solution) into the pericardium. All the dogs died unless the symptoms were relieved by a partial pericardectomy. They concluded that the symptoms were produced "by interfering with cardiac motion as a tightly fitting glove impairs the free movement of the hand," and not by the adhesions between the pericardium and the heart.

Myer⁹⁴ reported a case of purulent pericarditis in which the heart had ceased to pulsate when the pericardium was opened, and the simple manipulation of the heart was all that was necessary to start it.

Parlavecchio⁹⁵ found sixteen cases in the literature in which autopsies had revealed congenital absence of the pericardium, and in none of the cases was he able to trace any symptoms that could be attributed to the absence of the pericardium. He also completely removed the pericardium from a series of dogs and rabbits, and apparently there were no ill effects. From these observations, Parlavecchio concluded that the surgeon can feel safe in removing any amount of pericardium as far as the heart is concerned.

Naturally, the question has been raised concerning the recurrence of the adhesions and many various drugs and methods have been tried, both clinically and experimentally. None of these seem to have any great value and most surgeons simply bring the flap of muscle, etc., over the heart. However, Ochsner and Herrmann,⁹⁶ in 1929, submitted experimental evidence that a vegetable digestant in the pericardial cavity would prevent the reformation of adhesions. In Schmieden's seven cases, there was no instance in which symptoms could be ascribed to the recurrence of adhesions. Sufficient drainage is provided to insure the prevention of cardiac tamponade. This drainage should be placed at the cardiac apex.

REPORT OF CASE

History (abstract of case 21595, Jefferson Hospital).—A white man, aged 29, was admitted to the hospital on June 5, 1927. The family history was essentially unimportant. The following history was obtained: The patient had had the usual diseases of childhood, and had recovered promptly from each. There was no history of any condition that could be considered "rheumatism," and no history of an indefinite fever. He had had influenza eight years before admission, and had recovered apparently completely in two weeks. He had never had any other acute infections, nor any headaches. The eyes had been normal. He had had an indefinite earache in childhood. The teeth had been in excellent condition, with the exception of an alveolar abscess two years previously which "cleared up" in ten days following drainage. He had not had a sore throat nor any sores in the mouth.

He was subject to occasional colds, about one every winter, which lasted a week, and was accompanied with cough and expectoration of mucus. He had

⁹⁴ Myer, Willy: *Ann. Surg.* **73**:506, 1921.

⁹⁵ Parlavecchio, G.: *Deutsche Ztschr. f. Chir.* **98**:126 (March) 1909.

⁹⁶ Ochsner, A. and Herrmann, G. R.: *Experimental Surgical Relief of Experimentally Produced Pericardial Adhesions*, *Arch. Surg.* **18**:365 (Jan.) 1929.

had no chronic cough, hemoptysis, night sweats, palpitation, dyspnea and edema, and no pleural or precordial pain. His appetite and digestion had been good. He had never been troubled with nausea, vomiting or abdominal pain. The bowel movements had been regular, once daily, and the stools had never been bloody, tarry or clay-colored. The patient had never been jaundiced, and had never had hemorrhoids. The genito-urinary trace had been normal. The patient said he had never had a venereal disease.

He had been married ten years. His wife and three children (aged 9, 6 and 4 years) were living and well. Two children were born dead at term, one seven years ago and another five days ago. The cause of death was unknown, but the labors were difficult. There had been no miscarriage.

There had been no neuromuscular disorders.

The patient had never had any operations or injuries.

Before his present illness, he drank two cups of coffee daily. He did not use tea or alcohol, but chewed tobacco. He had weighed an average of 190 pounds (86.2 Kg.) his best weight being 196 pounds (89 Kg.). He thought that he had lost 20 pounds (9 Kg.) in the past three months.

Present Illness.—The patient was in excellent health up to three months before admission to the hospital or about February 1. At that time he was suddenly taken sick with severe cold, cough, fever and some chills, pains in the joints and general malaise. This was diagnosed influenza and he went to bed for a week. At the end of this time there was still some cough (but no expectoration). He felt much better, so got up and went to work. After another week the same symptoms recurred, but were somewhat worse than before; this time he remained in bed about ten days. Following this attack he was up for a week; then about the middle of March a severe earache developed in the left ear, which lasted eight days. He continued to feel weak and to have some cough until about four weeks previously, when on stooping over he suddenly felt a severe cutting pain and choking sensation in the retrosternal region. He said that it felt as though he would burst. At first the pain occurred only on stooping over, but later it would occur when he was in a recumbent posture, disappearing, however, after a few minutes rest. Soon after the onset of the choking, he saw a physician who gave him some medicine (digitalis), which he believed did him considerable good. He stayed in bed two weeks, at the end of which time the choking had entirely disappeared. At the time of admission he had fever, an occasional cough and marked weakness, but in general, he felt much better than he did two weeks earlier. There was a little expectoration of mucus, but he had noticed no blood at any time.

Examination.—The temperature was 101 F.; pulse rate, 96; respiratory rate, 22, and blood pressure, 118 systolic and 80 diastolic. The patient was a very well developed and fairly well nourished man who showed some loss of weight. He did not complain of any pain, and there was no cough or respiratory distress.

Skeletal examination gave negative results. There was no local or general glandular enlargement. The epitrochlear glands were not felt. The patient's face was somewhat flushed. The lips were a little pale, the nail-beds of good color, and there was no jaundice or cyanosis.

There was no tenderness of the sinuses. The sclerae were a little injected.

The pupils were equal and regular, reacted to light and contracted during accommodation. The ears were normal. The septum was intact and there was no nasal obstruction. The mouth was very dirty. The tongue was coated, and the breath had a bad odor. The tonsils were large and inflamed. The trachea was

slightly deviated to the right. There was no tracheal tug. The thyroid was not enlarged. The thorax was well developed and symmetrical. Expansion seemed a little greater on the right side.

On examining the lungs the percussion note was resonant on the right; on the left it was resonant posteriorly and at the apex anteriorly. Below the second rib and extending into the axilla was a large area of dullness continuous with the area of cardiac dullness. Vocal fremitus seemed normal. Breath sounds were vesicular throughout, but somewhat diminished over the dull area. After the patient coughed a few medium moist râles were heard just medial to the angle of the left scapula. The whispered and spoken voice was normal; there was no pectoriloquy.

Examination of the heart revealed that the point of maximal influence was just inside the nipple line in the fifth interspace. The apex was not well localized. There was no heave. There was no enlargement to the right, and no increase in the retromanubrial dullness. The left border of the heart was continuous with the dull area extending into the axilla. Sounds were faint. The heart rate was rapid but regular. No murmurs were heard.

The abdomen was soft, and no mass was felt. The edge of the liver was 5 cm. below the costal margin. The spleen was not felt, nor was any tenderness elicited.

The extremities were normal. The reflexes were equal and active.

Fluoroscopic examinations showed weak cardiac pulsations. The bases of both lungs were so filled with fluid as to prevent definitely outlining the diaphragm on either side. The position of the heart did not change with change of position of the patient, nor with either forced inspiration or forced expiration. No calcification of the pericardium was seen.

The blood was practically normal. Both Wassermann and Kahn reactions were negative. There was 50 mg. of nonprotein nitrogen per hundred cubic centimeters.

Course.—On June 14, 1927, 225 cc. of bloody fluid was aspirated from the pericardial cavity. Microscopic examination showed numerous red cells, "mainly crenated and otherwise deformed," and a few leukocytes. Guinea-pigs that received injections of the fluid gave negative results.

Between Feb. 1, 1927, and Nov. 30, 1927, the patient's pleural cavity was tapped by various physicians between eighty and ninety times. The largest amount of fluid removed at any one time was about 2,000 cc. The fluid removed from the pleural cavity was always of a clear amber color. Numerous specimens were examined in this hospital, but tubercle bacilli were never found. Inoculations into guinea-pigs gave negative results on five occasions—on four occasions when fluid from the pleural cavity was used and on one occasion when fluid from the pericardial cavity was used. The same type of fluid was also removed from the abdomen on several occasions (the patient was indefinite concerning the exact time and number). After one of these tapplings, the spleen was easily palpated.

Operation (November 30).—Ethylene anesthesia by the closed method was started at 10:15 a. m. and discontinued at 10:50 a. m. At the beginning of the operation, the pulse was ranging between 130 and 140 per minute. The blood pressure was taken every five minutes for two hours. Cartilaginous portions of the third, fourth, fifth, sixth and seventh ribs were removed with about an inch of the fourth, fifth and sixth ribs. In dissecting the pleura, a small opening was made in same by accident. A large quantity of amber colored fluid escaped from the pleura. After all fluid was removed, a purse string suture of chromic catgut was placed around the opening, and the lung expanded from the rebreathing bag, while the

purse string suture was tightened. There was no interference with respirations. About half of the sternum was removed with rongeurs and bone forceps. There were numerous adhesions between the pericardium, the thoracic wall and the diaphragm. Those between the pericardium and the wall of the chest were cut. At this stage of the operation, the pericardium came into easy reach. The thickened pericardium was opened at the apex over the left ventricle. The pericardium was about 1 cm. in thickness and very much resembled leather. There was practically no fluid in the pericardial cavity. Scissors were employed to enlarge the opening. As the opening was being enlarged, the heart began apparently to try to force its way out of the thick shell. Then a strip of pericardium about 2 by 7 cm. was removed. At this juncture, the heart was seen to be held at the apex by a strong band of adhesions. This was cut and did not bleed. After the cutting of this adhesion, it was easy to pass the finger around the ventricles. With great care, and with much fear, pieces of pericardium were removed from over the auricles and great vessels. These pieces of pericardium were "V" shaped and had the apex of the "V" toward the vessels. The walls of the coronary vessels looked very thin and care was taken not to disturb them. With the release of the heart, there was an almost instantaneous decrease in the pulse rate and an increase in the blood pressure. Before the patient left the operating room he expressed the greatest relief because he said he could feel that his "heart was free."

On his return to his room, relief and progressive improvement continued. His blood pressure and pulse rate continued in their improved condition. An electrocardiographic study was not made, because it was thought best to wait until he was well enough to go to the electrocardiographic room. He died suddenly on the seventh day after operation. Autopsy showed the heart free in the pericardial cavity. Sections of the myocardium showed many degenerative changes. Sections of the pericardium showed tuberculosis.

SUMMARY

1. The multiplicity of terms describing different operative procedures causes confusion.
2. A historical review and the results of the various operations in the literature up to 1930 are given.
3. As a postmortem observation, the condition has been recognized for many years.
4. Congenital defects of the pericardium have been found in sixty-four cases in which there was no history of any symptoms attributable to such defects.
5. Adherent pericarditis is found in about 4 per cent of routine necropsies.
6. "Acute rheumatic fever" of childhood is the chief etiologic factor, though tuberculosis and other organisms are frequently found to be the cause.
7. Six cases of primary tuberculous pericarditis have been reported in the literature since 1900.
8. There are ninety-six cases of calcareous pericarditis reported in the literature, and it is probable that such is the result of a tuberculous invasion.

9. The condition is far more frequent than it is usually thought to be.

10. Diagnosis is extremely difficult; careful history, physical examination, roentgenograms and electrocardiographs are of great aid.

11. Results of operations justify the plea for more frequent resort to surgical measures in spite of the difficulty of diagnosis.

12. Avulsion of the left phrenic nerve is advocated to supplement the Brauer operation, when the trouble is shown to be due to adhesions between the pericardium and the diaphragm.

13. A description of both the Delorme and Brauer operations is given.

14. A case is reported in which the Delorme operation was done; the patient died on the seventh day after operation.

NOTE.—Since this paper was submitted for publication, one additional case in which operation has been done for decortication of the heart has been located. My attention was called to this article by Dr. R. L. Payne of Norfolk.

The title of the article explains why this case was overlooked: "Sensibility of the Heart; A Human Experience," by George Waugh, William Willeox and Felix Rood. This article appeared in the *Lancet* 2:1054 (Nov. 21) 1925. The patient was 21 years old; the operation a remarkable success, and the patient in excellent condition five years after operation. The operation was done with local anesthesia (procaine hydrochloride and epinephrine), and the authors were much impressed with the lack of pain except with traction, on the pericardium. They compared their observation concerning the insensibility of the heart to the observations of Lennander (Uppsala) and Baker (London) concerning abdominal viscera which were made about twenty-five years previously.

Dr. Lawson and Dr. Gardner of Roanoke assisted in preparing the paragraphs concerning the electrocardiographic studies, and Dr. Peterson of Roanoke assisted in the preparation of references concerning the use of roentgenograms in the diagnosis of adherent pericarditis.

A RARE CONGENITAL DEFICIENCY OF THE PERICARDIUM *

JAMES CRAWFORD WATT, M.D.
Professor of Anatomy, the University of Toronto
TORONTO, CANADA

The specimen presented is that of a very rare anomaly, showing congenital absence of a separate pericardial sac, the heart being contained in the same serous cavity as the left lung. It was obtained by Dr. W. A. Burr, who was called to the city morgue to undertake the postmortem examination of a middle-aged man who had died suddenly. When the thorax was opened, Dr. Burr was surprised to find the heart and the left lung occupying a common cavity. As he realized the rarity and value of what he had found, he removed all the thoracic viscera, the diaphragm and what remained of the pleural sacs en masse and presented the specimen to the department of anatomy of the University of Toronto.

REPORT OF CASE

The man from whom these viscera were obtained was aged 52, of medium height and well developed. He was unmarried and lived alone and not much was known of his habits. The night of his death he was visiting a friend. As he felt unwell he arose to go into another room and dropped dead. From his friend it was learned that for about one year previous to his death he had suffered occasionally from attacks of weakness. He had led a normal, active life, and, except during the last year, he had not complained of any weakness or disability and had been regularly employed in fairly heavy work. Lately his occupation had been that of operator of a machine in a box factory.

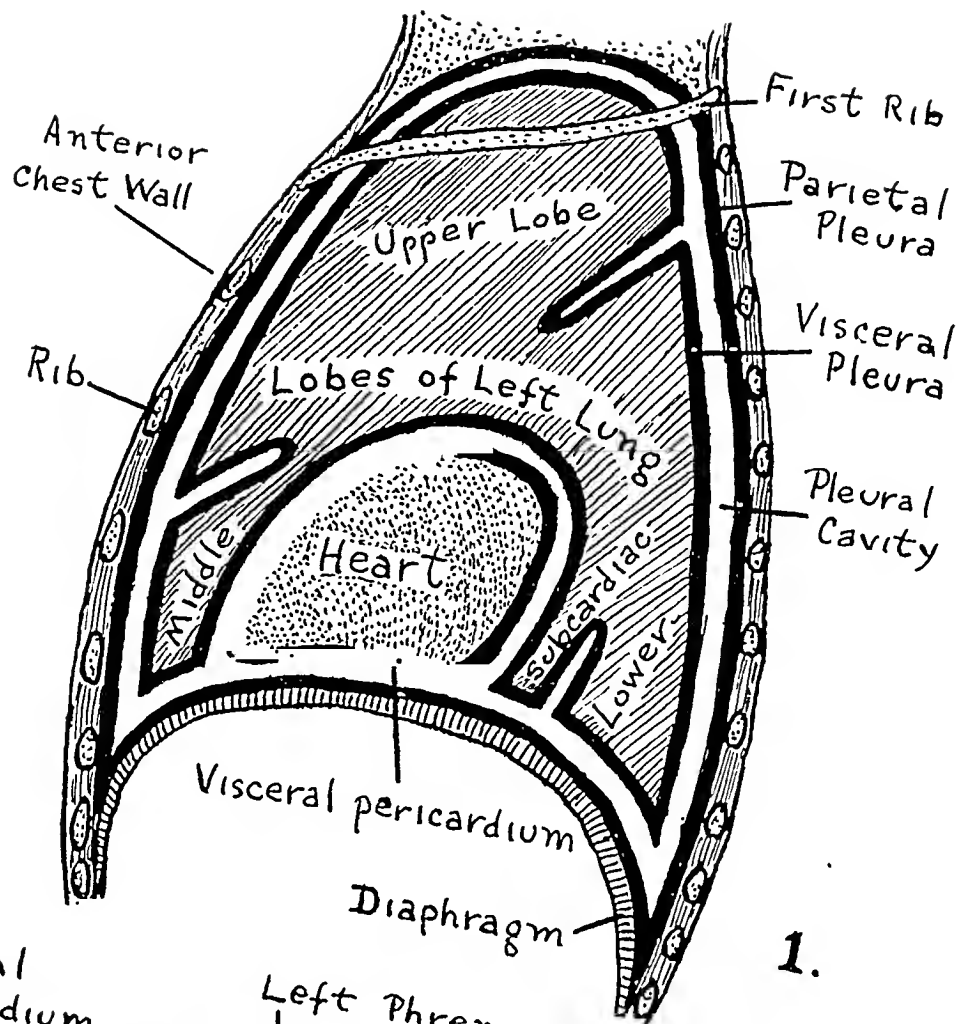
The cause of death found at postmortem examination was thrombosis of the anterior descending branch of the left coronary artery with an accompanying area of soft, degenerated, ventricular muscle.

The specimen, when brought to the laboratory, was placed in a diluted solution of formaldehyde, U. S. P. (1:10) for hardening and preservation. In one mass were the thoracic contents: heart and great vessels, trachea, esophagus, both lungs and the diaphragm, nerves, vessels, glands and parts of both pleural sacs. Each of the latter had been fully opened anteriorly, and most of the costal pleura was lacking.

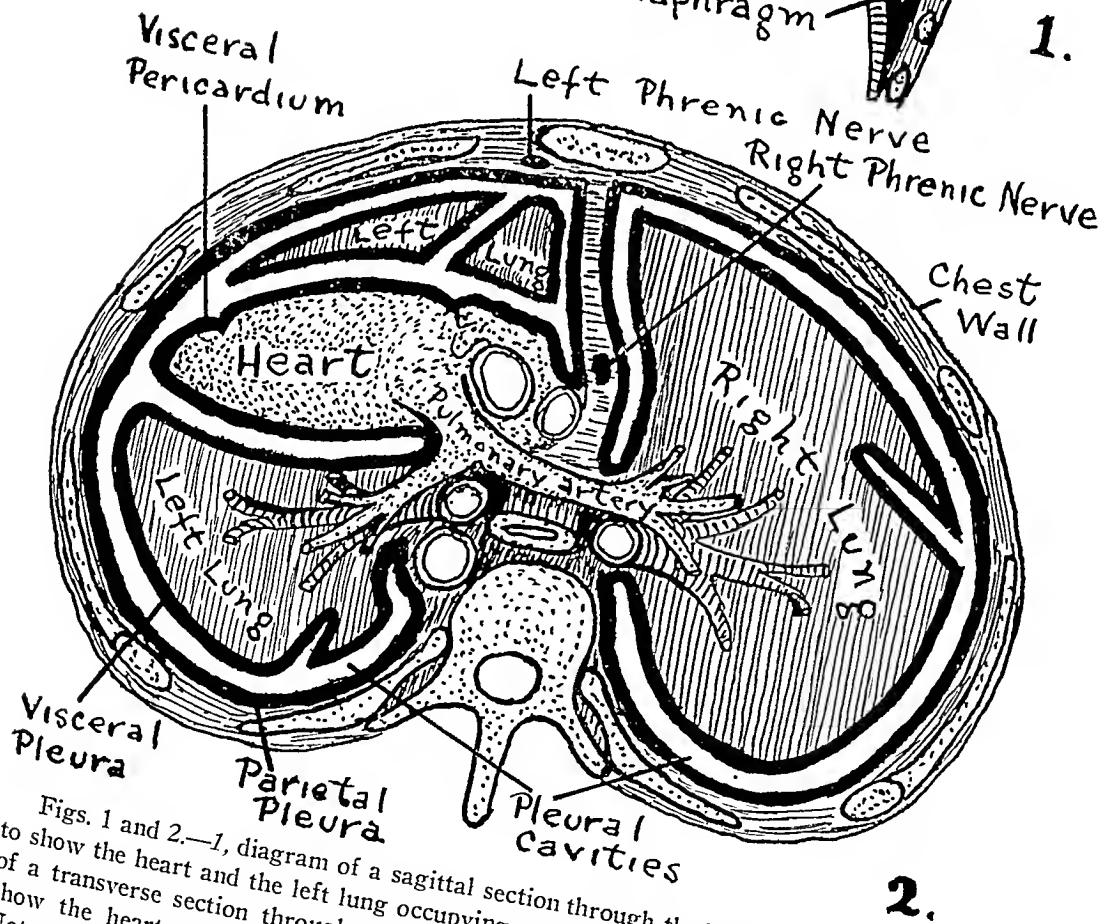
After preservation was completed, photographs of the viscera were taken from various aspects (figs. 7 to 10), and the specimen was then thoroughly studied.

The heart was of moderate size, being somewhat longer than usual (fig. 8), and had a sharp pointed apex. The organ was shaped like a long, narrow cone, and was placed much more horizontally in the thorax than is usual. It lay

* Submitted for publication, Feb. 24, 1931.

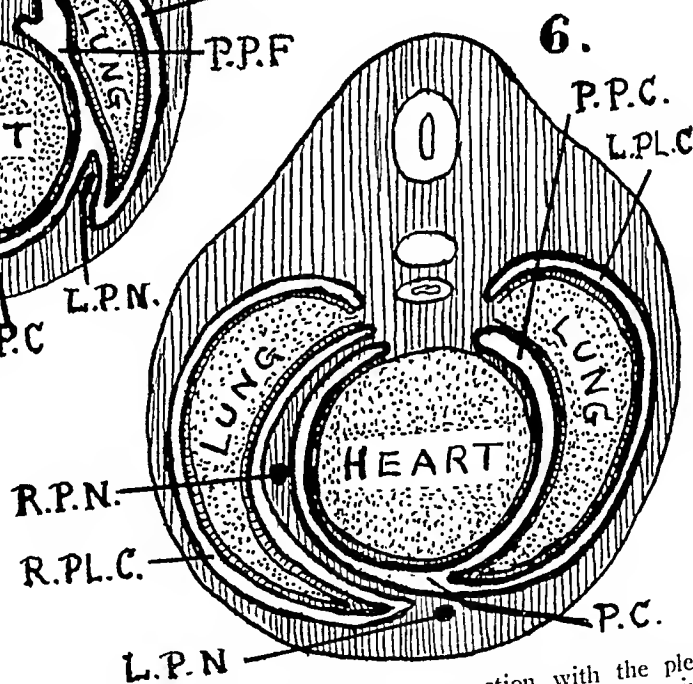
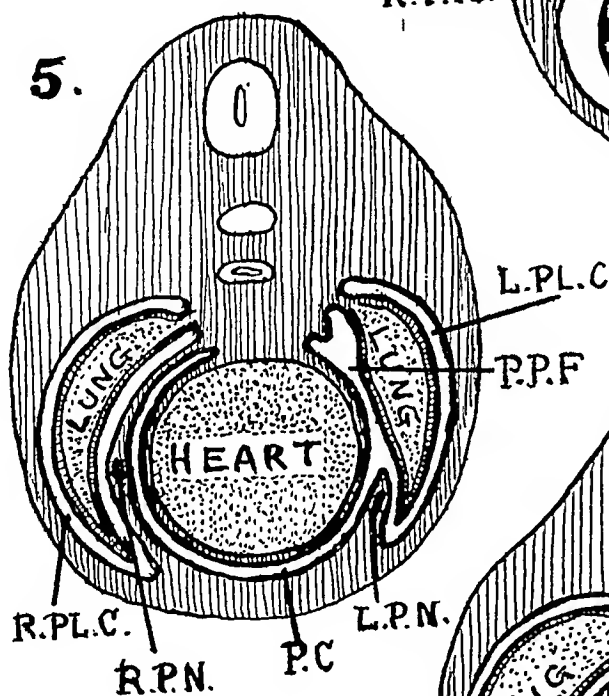
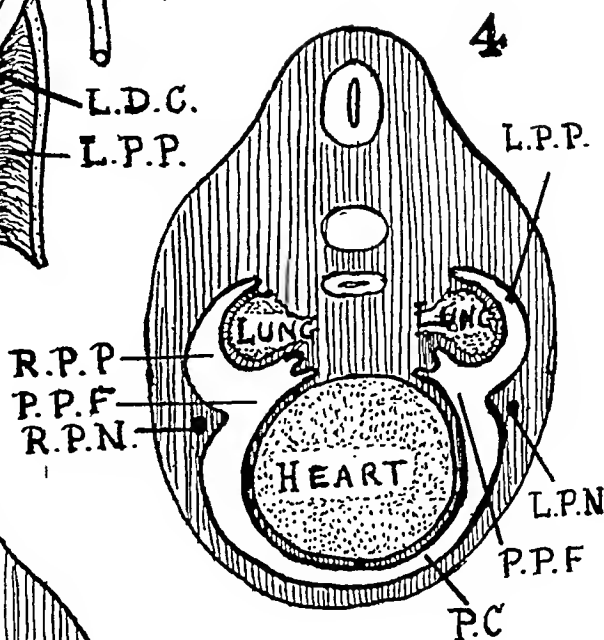
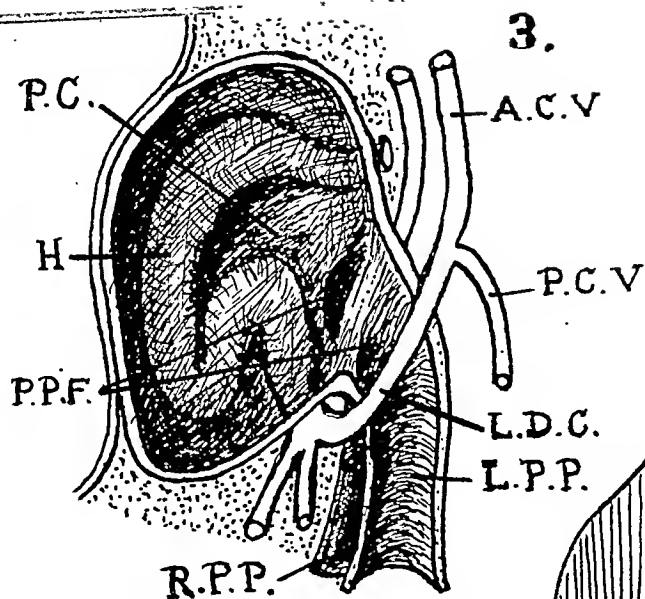


1.



2.

Figs. 1 and 2.—1, diagram of a sagittal section through the left side of the thorax to show the heart and the left lung occupying a common visceral cavity. 2, diagram of a transverse section through the thorax at the level of the root of the lung to show the heart and the left lung occupying the same common visceral cavity. Note the reflection of the serous membrane over the various organs and also the position of the left phrenic nerve. The lung lying in front of the heart joins the remainder of the organ just above the level of this section.



Figs. 3 to 6.—3, diagram of the pericardial celom and its connection with the pleuroperitoneal passages in a young human embryo. The lung invaginates the pleuroperitoneal passage just below the duct of Cuvier. 4, 5 and 6, diagrams of transverse sections of embryos, designed to show successive stages in the failure of the pleuropericardial foramen to close on the left side, thus producing the anomaly described in this paper. 4, appearance of the lung bud; the pleuropericardial foramen is open on both sides. 5, the lung growing forward at the side of the heart; the pleuropericardial foramen is closed on the right and is still open on the left side. 6, the lung now surrounds the heart, the left pleuropericardial foramen is still open and fully dilated, the lung and the heart occupying one common cavity, with the left phrenic nerve pushed forward to the anterior wall of the chest. A.C.V. indicates the anterior cardinal vein; H, the heart; L.D.C., the left duct of Cuvier; L.P.L.C., the left pleuroperitoneal passage; P.C., the pericardial cavity; L.P.N., the left pleural cavity; L.P.P., the left pleuroperitoneal passage; P.C.V., the posterior cardinal vein; P.P.F., the pleuroperitoneal foramen; R.P.L.C., the right pleural cavity; R.P.N., the right pleural cavity; R.P.P., the right pleuroperitoneal passage.

right on the diaphragm and extended directly out to the left, and it was so overlapped by the left lung (fig. 7) that only the right atrium and the apex were visible. The apex came to the surface far out to the left between two lobes of the lung. Just medial to the apex was a deep notch (fig. 9) between the right and left ventricles, so that the apex region appeared almost bifid.

There was no fold or partition (fig. 8) to indicate division of the serous cavity in which the heart and left lung were placed. The heart and the left lung possessed smooth, shining, serous surfaces free from adhesions, and one large

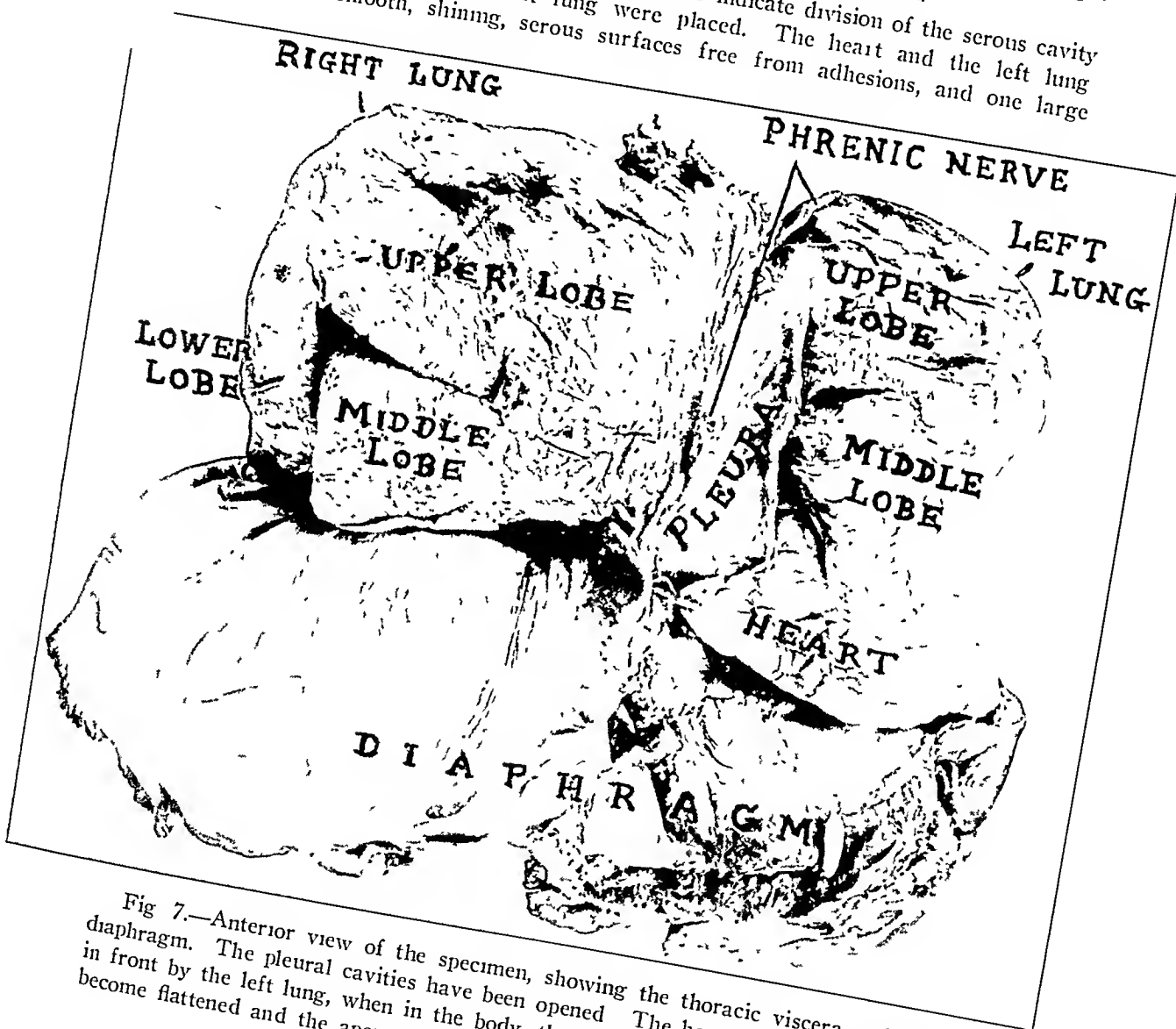


Fig 7.—Anterior view of the specimen, showing the thoracic viscera and the diaphragm. The pleural cavities have been opened. The heart was more covered in front by the left lung, when in the body, than is shown here. The lungs have become flattened and the apex on each side rounded during preservation.

parietal serous covering on the wall of the chest (fig. 1) was continuous with the visceral surfaces, completing the cavity containing both organs. Owing to the fact that most of the heart was hidden by the overlying lung, one is naturally inclined to call this a pleural cavity at first sight. The cavity, as will be shown later, was developmentally a combined pericardial and pleural one, or a pleuropericardium.

The visceral pericardium invested the heart as usual and was reflected off this organ at the entrance or exit of the great vessels. Behind the aorta and pulmonary artery was the usual tunnel-like passage from side to side known as the transverse sinus (figs. 8 and 10), which had the great veins behind it. In this case, the sinus was situated with its axis running down to the right, owing to the fact that the heart was turned so much more than normally into the horizontal plane to the left.

The oblique sinus of the pericardium (figs. 9 and 10) was also found behind the heart, opening to the left. This sinus, which is bounded by the reflection of

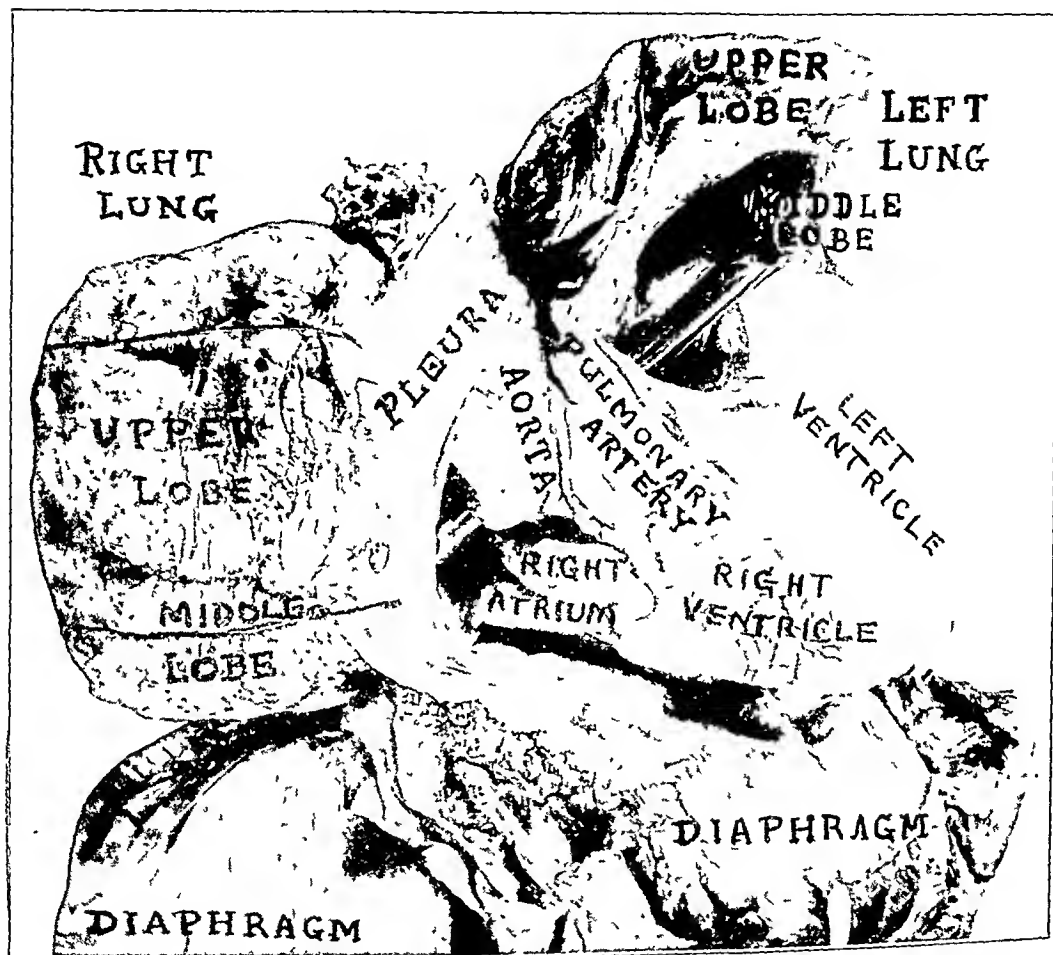


Fig. 8.—Anterior view—the upper part of the left lung has been lifted to expose the heart. The anterior part of the left pleura has been drawn over to the right. The metal rod passes through the sinus transversus.

pericardium off the heart at the entrance of the great veins, usually has a wide opening inferiorly and to the left. In this case, however, the opening was quite narrow, admitting only one finger, but the sinus broadened out somewhat in its interior.

From the anterior surface of the left pulmonary artery and veins, the pericardium turned directly to the root of the left lung (figs. 2 and 10) to form the visceral pleura. Behind the root, the pleura was continuous from the bronchus and vessels with the wall of the sac. Below the root of the lung, a thin reflection

of serous membrane (figs. 9 and 10) was continued off the heart as far down as the surface of the left ventricle posteriorly, and also a small area of the diaphragm on to the medial surface of the lung below the root. This fold was interpreted as the lateral ligament of the lung. It was responsible for narrowing the entrance into the oblique sinus by extending for some distance below the left pulmonary veins.

The parietal part of this serous sac was applied to the side of the vertebrae, the inner surface of the ribs and the back of the sternum. At the midline behind the sternum it turned dorsally (figs. 2, 7 and 8) and passed back toward the

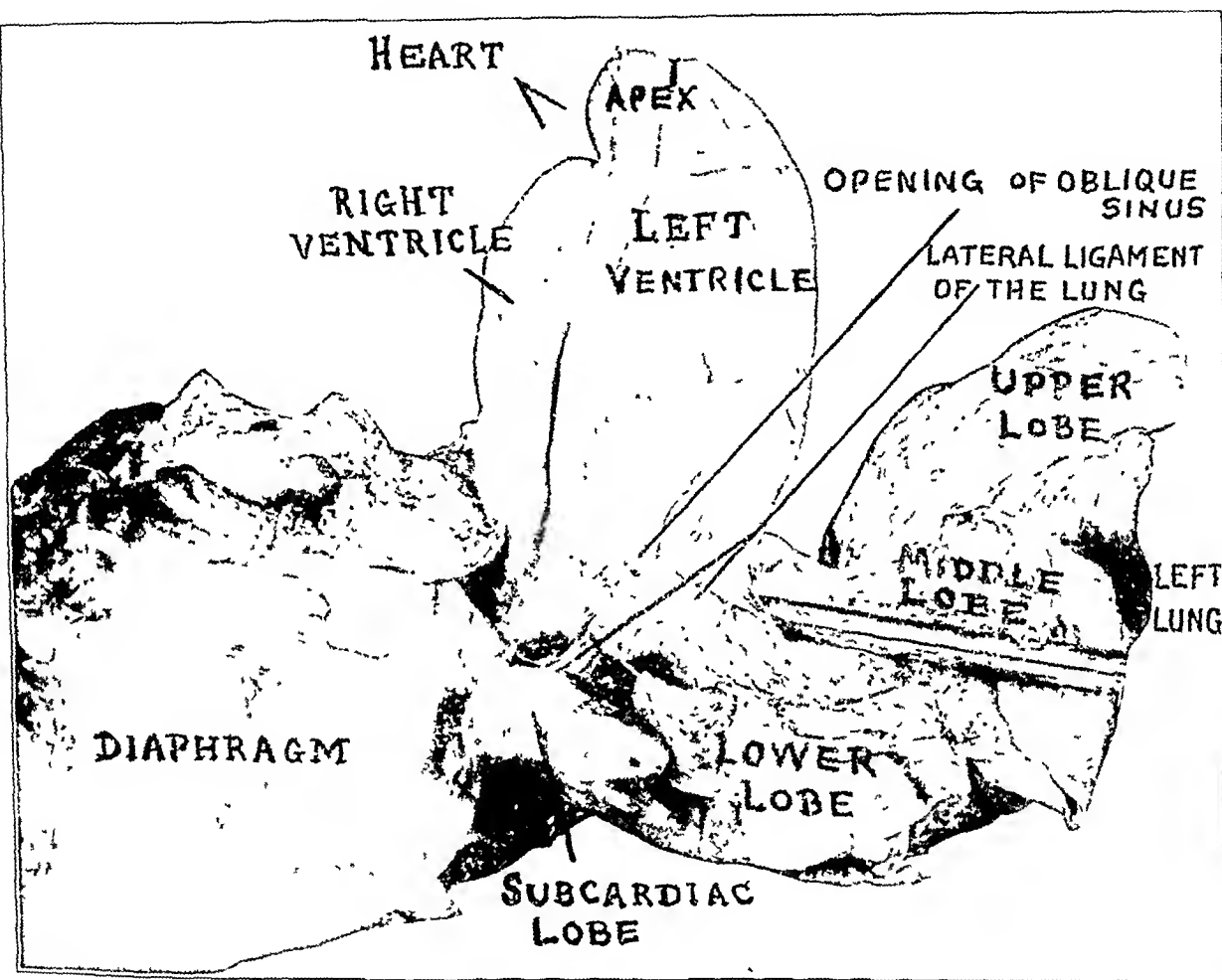


Fig. 9.—View from the left and somewhat inferiorly. The left lung has been drawn away from the heart, and the heart has been elevated so as to show its postero-inferior portion. The metal rod runs into the sinus transversus.

heart, lying in direct contact with the corresponding portion of the right pleura. The diaphragm was covered on its upper surface right up to the midline, where the right and left pleurae, in contact with each other, were reflected to form the mediastinal portion. The cervical dome was normally placed. The right pleura showed a normal disposition.

The left lung was most interesting in its arrangement. Fissures passing right into the hilus cut it into four distinct lobes, of which the upper two lay above and in front of the heart (figs. 1 and 7) and the lower two (figs. 1, 9 and 10)

behind the heart. These four were named the upper, middle, lower and subcardiac lobes. The upper and middle lobes corresponded with the upper lobe usually seen on the left side, the fissure between them corresponding with the intermediate fissure normally found on the right side, and sometimes on the left, separating the normal middle lobe from the upper lobe.

The lobe called the subcardiac was separated by a deep fissure from the lower lobe, in relation to which it lay posteromedially, and was in contact with the

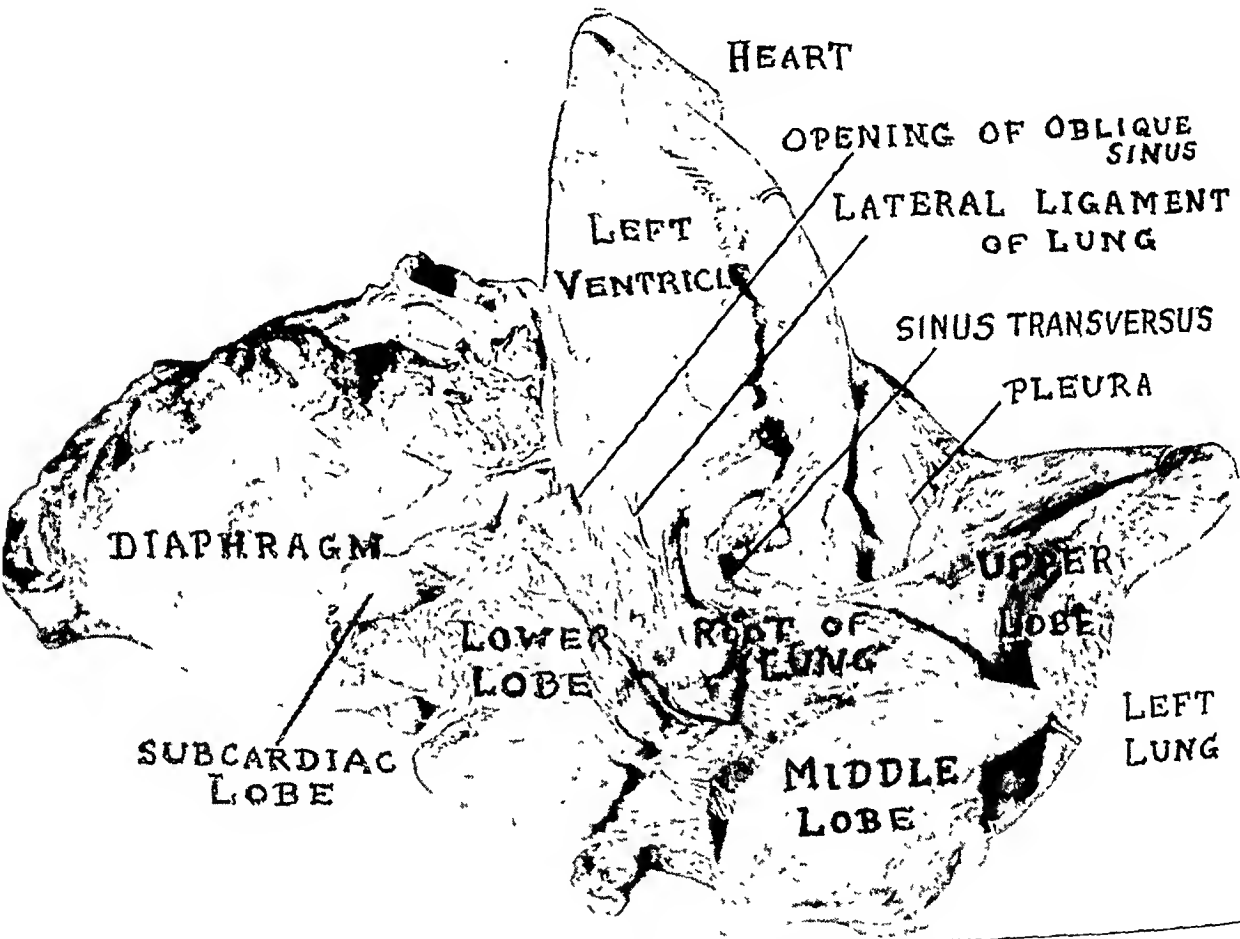


Fig. 10.—View from the left and somewhat superiorly. The left lung has been drawn away from the heart, and the heart has been elevated.

curved posterior surface of the heart. The lower edge of this lobe therefore insinuated itself slightly between the heart and the diaphragm.

The right lung, which was larger than the left, was divided into the usual three lobes, upper, middle and lower.

The right and the left vagus nerves were normal in position and arrangement. As they passed behind the roots of the lungs and on the esophagus, a disturbance of their course was not to be expected.

The right phrenic nerve (fig. 2) also followed the usual course, lying in front of the root of the right lung, and then passing down over the right side of the

heart in the connective tissue between the mediastinal walls of the right pleura and the left pleura (or pleuropericardium).

The left phrenic nerve (figs. 2 and 7) was greatly displaced, for instead of lying in the mediastinum it had been forced out into contact with the wall of the chest and was lying outside the parietal pleura against the deep surface of the sternum.

COMMENT

The condition just described is extremely rare, and all cases except one or two have been found in human beings; the others were found in dogs.

Moore reviewed the literature to 1925; including the case described by him, there were sixty-four cases on record at this time. He stated that the first case of absence of the pericardium to be reported was described by Realdus Columbus in 1559, but it was not believed until a second case was reported by Baillie in 1788. In 1874, there were ten cases; in 1910, there were thirty-two cases on record, and in 1925, they totalled sixty-four. One additional case was reported by Grant in 1927, and my case now makes the sixty-sixth.

Moore classified forty-two cases, which were well described, as follows:

Group 1: Heart and left lung in one serous cavity, 59.5 per cent.

A. With complete absence of separate pericardium.

B. With rudimentary folds or other evidence of partly separate pericardium.

Group 2: Heart occupying a pericardial cavity that had a foramen into the left pleural cavity, 21.4 per cent.

Group 3: Heart lying between the right and the left closed pleural cavities, in connective tissue, without a pericardium or only a rudiment at the base of the heart, 19.1 per cent.

Several cases in the last group showed undoubted evidence of being produced by an obliterative adhesive pericarditis. The present case would be classed under group 1A.

The production of the anomaly in the cases in which there is a serous cavity has been explained by various authors (see Moore) in several ways, but it seems to me that there should be no doubt in the matter, as it can be explained naturally on purely embryologic grounds.

It will be remembered that at a certain stage of development (figs. 3 and 4) there is a well marked pericardial cavity still connected by a pleuropericardial foramen on each side to the corresponding pleural cavity. At about the same level, each pleural cavity is also connected by the pleuroperitoneal passage to the peritoneal cavity.

On its way to the heart, the duct of Cuvier runs in a fold which lies lateral to the pleuroperitoneal passage, and from the fold a partition grows ventrally to close the pleuropericardial foramen, while another one grows dorsally to close the pleuroperitoneal passage. The failure of the ventral partition to appear would leave the communication between the

pericardial and pleural cavities open (fig. 5). If the defect were of sufficient size, part of the heart could protrude through this opening and would lie in the pleural cavity, giving rise to the cases classified as showing a partly absent pericardium.

If the heart remained in its cavity and part of the lung growing ventrally insinuated itself into the pleuropericardial foramen and forced its anterior margin forward ahead of it, the foramen would be dilated gradually until the surfaces of the pleura and pericardium would have no fold or division between them and the two cavities would be fully opened up into one large combined cavity (fig. 6) holding both the heart and the left lung, as seen in the case reported.

The phrenic nerve lies in the connective tissue between the pericardial and pleural membranes, in the anterior border of the foramen between the two cavities, so that on dilatation of the foramen the nerve is carried forward. If the dilatation is complete, as it was in the case described, the nerve is finally forced sufficiently forward to be in contact with the deep surface of the anterior wall of the chest (figs. 2, 6 and 7), which is the position in which the nerve was found in this specimen.

In only one instance is there a record of the opening persisting between the pericardium and the right pleural cavity, and this was in the case of the dog described by Moore. The almost universal occurrence of this anomaly on the left side is associated with the early disappearance of the left superior vena cava. If this occurs too early, it can easily be conceived that it may interfere with the closure of the opening alongside of which it lies. The failure of closure on the right side in one case, however, shows that even the continued presence of the vein will not absolutely guarantee the appearance and development of the normal partition that closes the aperture. Once the opening fails to close, the presence of either the heart or a lung in it will enlarge it greatly and expand it so that the two cavities become more or less completely one.

In reference to age, the cases reported show the widest variations as this anomaly has been found not only in fetuses but in many adults. In twenty cases in which exact clinical knowledge as to the condition of the heart was obtainable (tabulated by Grant), the youngest patient was 20, and the oldest 62 years of age. The anomaly is thus not incompatible even with the attainment of old age.

The records also show that the lack of a separate pericardium does not necessarily make the person so affected weak or debilitated, for many of these persons showed robust good health and participated in strenuous activity. The patients whose cases were listed were soldiers, masons, laborers and office workers. The man whose case is the subject of this paper was active and hard working, and he reached the age of 52.

Sex does not seem to have a bearing on the production of the anomaly, which was exhibited by members of both sexes of various ages.

The causes of death were not always cited for the different cases, but when noted they often had no reference to any special condition of the heart and consisted of such diseases as syphilis, nephritis, pneumonia and carcinoma.

Enlargement of the heart was present in ten of the twenty most accurately recorded cases, but not all of the patients died of heart failure; it was not present in the other ten cases. Thus, even with absence of a separate pericardial sac to support the heart it is not essential for a person living an active life to have hypertrophy to possess a heart strong enough to support him. The heart was not enlarged in the case forming the subject of this paper.

In view of its character as a serous membrane, the pericardium acts as a bursa to the heart and provides a free and almost frictionless surface for its movements. However, owing to the strong fibrous layer in the parietal pericardium, it has long been believed and widely taught that the pericardium exerts a supporting and restraining influence on the heart, preventing undue dilatation in times of sudden strain. Of course, long-continued or steadily applied strains will dilate the pericardium, and the supporting action is done away with under such conditions, for it acts to advantage only under stresses of short duration. Thus it is that the pericardium does not prevent the dilatation of a heart the myocardium of which is weakening.

Hauffe expressed the belief that during systole, or contraction, of a cardiac chamber, the wall of the heart tends to be withdrawn from the parietal pericardium. This creates a negative pressure in the pericardial cavity, which helps the diastole or expansion of the filling chamber, as it tends to expand this chamber and suck blood into it. In this way, he looked on the heart and pericardium as a combined force and suction pump.

In the series of cases recorded with absence of the pericardium, there were many persons who lived active lives entailing considerable physical exertion; they did not show signs of cardiac weakness, nor did they have hearts larger than normal. In these cases the heart was in the same cavity as the left lung. The lung could not replace the pericardium either in its function as a restraining influence on dilatation or as something to provide suction to help dilate the chambers in each diastole, for the lung is too yielding and lacking in resistance. Both of these functions would be interfered with in such cases, as the lung would yield and neutralize any change of pressure that was created.

Therefore, it follows that a separate pericardium is not an essential part of the mechanism of the heart. It serves primarily neither for support of the heart nor to provide aid in keeping up the circulation, but acts

primarily as a serous membrane the important function of which is to provide a practically frictionless bursa that will facilitate the movements of the heart. This function can also be accomplished quite well with the heart in the pleural cavity.

CONCLUSIONS

A specimen is described taken from a man, aged 52, who exhibited a rare congenital anomaly in which the heart and the left lung occupied a common serous cavity.

This common cavity was produced in embryonic development by a combining of the pericardial and the left pleural cavities, through failure of the left pleuropericardial foramen to close, followed by its subsequent dilatation.

The left lung exhibited four lobes.

The left phrenic nerve lay in contact with the deep surface of the anterior wall of the chest.

The failure of the pleuropericardial foramen to close was probably associated with the changes accompanying the disappearance of the left superior vena cava.

This is the sixty-sixth case of its kind recorded in 371 years.

This condition is not incompatible with a long, active life, free from any special weakness of the heart.

A separate pericardium is not absolutely essential to the normal functioning of the heart.

The main function of the pericardium is to provide a nearly frictionless serous sac to facilitate the movement of the heart.

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METAPHEN AS A DISINFECTANT OF THE SKIN*

JOHN A. KOLMER, M.D.

AND

MALCOLM J. HARKINS, V.M.D.

PHILADELPHIA

During the past year Raiziss, Severac and Moetsch¹ reported that solutions of metaphen, applied on gauze for five minutes in strengths ranging from 1:500 to 1:2,500, produced complete sterilization of the skin of rabbits contaminated with broth cultures of *Staphylococcus aureus*, *Streptococcus hemolyticus* and *Bacillus subtilis* after preliminary cleansing. White and Hill,² however, questioned the results on the basis that the drug was transferred from the skin to the subcultures in amounts sufficient to inhibit bacterial growth in the medium, thereby leading to the erroneous supposition that metaphen had completely sterilized the skin. Since they stated that metaphen in the dilution 1:500 cannot be relied on regularly to sterilize normal human skin after an exposure of five minutes, and since the subject of disinfection of the skin is one of great practical importance, especially in relation to surgery, we have thought it advisable to repeat the experiments of these workers in order to determine the possible sources of discrepancy in their reports and in an effort to fix the exact status of metaphen as a disinfectant of the skin.

Our experiments with rabbits were conducted as described by Raiziss, Severac and Moetsch. The hair of the abdomen was removed with a weak solution of barium sulphide, followed by a cleansing of the skin with soap and water and the application of metaphen in the dilution 1:1,000 for five minutes, followed by the administration of alcohol and ether. The skin was then contaminated with a mixture of equal parts of broth cultures of *Staphylococcus aureus*, *Streptococcus hemolyticus* and *B. subtilis* and allowed to dry. Cultures were invariably positive, indicating the presence of viable organisms.

Sterile gauze was then saturated with metaphen in the dilutions 1:500 and 1:2,500 and applied for five minutes, and cultures were made by rubbing the areas for thirty seconds with sterile swabs moist-

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* From the Research Institute of Cutaneous Medicine.

1. Raiziss, G. W.; Severac, Marie, and Moetsch, J. C.: Metaphen as a Germicide and Skin Disinfectant, J. A. M. A. **94**:1199 (April 19) 1930.

2. White, E. C., and Hill, J. H.: Inefficiency of Metaphen as a Skin Disinfectant, J. A. M. A. **95**:27 (July 5) 1930.

ened with sterile broth. The tip of each swab was then clipped and dropped into bouillon.

As stated, White and Hill contended that the swabs may carry enough metaphen into tubes containing 10 cc. of broth to prevent bacterial growth. If this were true, it is likely that cultures of the skin with moistened swabs held horizontally would pick up and transfer more metaphen than swabs held vertically. Therefore, we cultured the skin in both ways by rubbing for thirty seconds and inoculated not only tubes carrying 10 cc. of broth, but likewise flasks carrying 100 and 900 cc., the latter as employed by White and Hill, to dilute any metaphen carried over on the swabs beyond the bacteriostatic threshold.

All of our subcultures into tubes containing 10 and 100 cc. of broth were sterile, while some in 900 cc. gave growths. Off-hand this would indicate that the swabs had transferred bacteriostatic amounts of metaphen to the tubes containing 10 and 100 cc. of broth, but when these were inoculated with 4 mm. loopfuls of a twenty-four hour broth culture of *Staphylococcus aureus* at the end of seventy-two hours, all gave heavy growths.

At the same time, we applied metaphen in the dilutions 1:500 and 1:2,500 on squares of gauze to the skin of the under surface of the forearm of two laboratory workers, as described by White and Hill; five minutes later we rubbed the wet areas for fifteen seconds with swabs held vertically and horizontally and then clipped these with sterile scissors into tubes containing 10, 100 and 900 cc. of broth. Again the cultures 10 and 100 cc. showed no growth, while some of those of 900 cc. developed growths of *B. proteus* and *B. subtilis*. However, when the subcultures of 10 and 100 cc. were inoculated with *Staphylococcus aureus* at the end of seventy-two hours, heavy growths of this organism developed. Furthermore, when the 10 and 100 cc. of broth were inoculated with *Staphylococcus aureus* immediately after the cultures were taken from the skin, growth developed as promptly and as heavily as in the controls, without exhibiting any demonstrable degrees of bacteriostatic activity due to metaphen carried over on the swabs.

In this, however, we had a perplexing situation in that our subcultures of 10 and 100 cc. showed no growths and did not exhibit bacteriostasis when inoculated with 4 mm. loopfuls of twenty-four hour broth culture of *Staphylococcus aureus*, while some of the subcultures of the skin in 900 cc. showed heavy growths.

Because of these paradoxical results, we then tested the skins of twenty additional subjects from the laboratory personnel. The forearms were chosen, and preliminary cleansing was not employed. Four thicknesses of sterile gauze (5 by 8 inches [12.7 by 20.32 cm.]) were saturated with metaphen in the dilution 1:500 in a pan and were accurately applied to the skin for exactly five minutes as timed with a stop

watch. Cultures were then made of the wet areas with sterile swabs held vertically and whirled about for ten seconds, followed by clipping of the ends with sterile scissors into tubes containing 10 cc. of broth and flasks containing 100 and 900 cc. In each case, two cultures were made into 900 cc. of broth contained in the usual wide-mouthed Erlenmeyer flasks and in the narrow-mouthed volumetric flasks, in order to reduce to a minimum the chances of contamination with air from the opening and closing of the latter. At the end of seventy-two hours of incubation, the subcultures showing no growths were inoculated with 4 mm. loopfuls of twenty-four hour broth culture of *Staphylococcus aureus* as a test for the presence of bacteriostatic amounts of metaphen. All cultures showing "no growths" were kept under observation at 37.5 C. for ten days. The results are summarized in the accompanying table as follows:

1. Cultures were taken from all of the skins with swabs and placed in tubes containing 10 cc. of broth before metaphen was applied. All gave growths of various organisms, including *Staphylococcus albus*, *B. proteus*, *B. subtilis*, *B. pseudodiphtheriae*, *B. coli* and *Sarcinae*.

2. After the application of metaphen, all of the subcultures in tubes containing 10 cc. of broth were sterile after seventy-two hours of incubation. These were then inoculated with 4 mm. loopfuls of twenty-four hour broth culture of *Staphylococcus aureus*, and all gave good growths.

3. Six, or 30 per cent, of the subcultures in the flasks carrying 100 cc. of broth from the twenty subjects gave growths including *Staphylococcus albus*, *B. subtilis*, *B. pseudodiphtheriae* and *Sarcinae*. When the remaining 14, or 70 per cent, sterile cultures were inoculated with *Staphylococcus aureus* at the end of seventy-two hours, all gave good growth.

4. Eight, or 40 per cent, of the subcultures from the twenty subjects gave growths in the wide-mouthed Erlenmeyer flasks containing 900 cc. of broth, including *Staphylococcus albus*, *B. subtilis*, *B. pseudodiphtheriae* and *Sarcinae*. When the remaining 12, or 60 per cent, of sterile cultures were inoculated with *Staphylococcus aureus* at the end of seventy-two hours, all gave good growth.

5. Five, or 25 per cent, of the subcultures from the twenty subjects gave growths in the narrow-necked volumetric flasks containing 900 cc. of broth of the same organisms. When the remaining fifteen, or 75 per cent, of the sterile cultures were inoculated with *Staphylococcus aureus* at the end of seventy-two hours, all gave good growths.

The occupations of the subjects tested had some influence on the results, in that those engaged in "dirty" work as laboratory cleaners (nos. 5, 7, 9 and 19) showed heavier growths than the remaining subjects, who were mostly technicians and members of the staff. Indeed,

before the application of metaphen, cultures from two of the latter did not show growths and therefore are not included in the series; however, it was apparent that the number and kinds of bacteria on the skin had some influence on the results, and for this reason tests of these kinds conducted in different laboratories cannot be expected to give more than approximately similar results. Furthermore, it would appear that the

Metaphen in Aqueous Solution as a Disinfectant of the Skin

No	Culture of Skin	Results of Cultures After 1.500 Metaphen for Five Minutes			
		In 10 Cc of Broth	In 100 Cc of Broth	In 900 Cc of Broth, Erlenmeyer Flask	In 900 Cc of broth, Volumetric Flask
1	Staphylococcus; B subtilis	No growth	Staphylococcus	Staphylococcus	No growth
2	Staphylococcus	No growth	No growth	No growth	No growth
3	Staphylococcus; Sarcinae	No growth	No growth	Staphylococcus B	No growth
4	B subtilis; B proteus	No growth	Staphylococcus; Sarcinae	Sarcinae	Sarcinae
5	Staphylococcus; B subtilis	No growth	Staphylococcus	Staphylococcus	Sarcinae
6	Staphylococcus; Sarcinae	No growth	No growth	No growth	No growth
7	B pseudodiphth; Staphylococcus	No growth	No growth	B pseudodiphth	B pseudodiphth
8	Staphylococcus	No growth	B pseudodiphth; B subtilis	B subtilis; B proteus	B subtilis
9	B proteus; B pseudodiphth.	No growth	B pseudodiphth; B subtilis	B subtilis; B proteus	B subtilis
10	Staphylococcus	No growth	No growth	No growth	No growth
11	Staphylococcus	No growth	No growth	No growth	Staphylococcus
12	Staphylococcus; B pseudodiphth	No growth	B pseudodiphth	No growth	No growth
13	Staphylococcus	No growth	No growth	No growth	No growth
14	Staphylococcus	No growth	No growth	No growth	No growth
15	Staphylococcus; B proteus	No growth	No growth	Staphylococcus	No growth
16	Staphylococcus	No growth	No growth	No growth	No growth
17	Staphylococcus; B pseudodiphth.	No growth	No growth	B pseudodiphth	No growth
18	Staphylococcus	No growth	No growth	No growth	No growth
19	Staphylococcus; B coli; B subtilis	No growth	B subtilis	No growth	No growth
20	Staphylococcus; B subtilis	No growth	No growth	No growth	No growth

bacterial flora varies in different localities of the skin even within a small space, or, at least, that the organisms recovered in cultures may vary, probably due in part to their different depths in the skin. For this reason, tests conducted with the skins of rabbits first prepared by scrubbing with soap and water followed by the application of alcohol and ether and contamination with broth cultures of bacteria may be expected to yield more consistent and more favorable results, since most of the bacteria are on the surface of the skin instead of being located at varying depths.

SUMMARY

Owing, therefore, to the variables inseparably associated with tests of these kinds, only broad conclusions are justified. All things considered, it has appeared to us that in the method employed, in which subcultures are made with swabs, at least 100 cc. of broth is required instead of 10 cc. Probably narrow-necked volumetric flasks carrying 900 cc. of broth are most acceptable and suitable for the purpose of still further diluting any disinfectant carried over on the swabs beyond the bacteriostatic threshold and for reducing contamination with air to a minimum, although the large size and the large amounts of medium required constitute technical objections when many tests are to be conducted and when 100 cc. would appear to be sufficient. Dilution, however, is the chief factor since with proper care and technic contamination with air can be largely, if not entirely, prevented. As a matter of fact, we opened a number of flasks in the same manner and for the same period of time as required for making the cultures and in no instance did any of these controls show bacterial growths. The use of large amounts of broth for subculturing is especially required when one is testing such a powerful bactericide as metaphen, which Raiziss and his colleagues found bacteriostatic for *Staphylococcus aureus* in dilutions as high as 1:20,400,000.

The results have indicated, therefore, that the 100 per cent "no growths" of subcultures in 10 cc. of broth may have been due in part to the presence of bacteriostatic amounts of metaphen carried over on the swabs, as stated by White and Hill, although we had no direct evidence of this, since all of the cultures seeded seventy-two hours later with *Staphylococcus aureus* yielded good growths. We surmised that some change may have occurred during the seventy-two hours of incubation whereby the bacteriostatic activity of the metaphen was removed, but in separate tests not included in the foregoing the subcultures in 10 cc. of broth were seeded with *Staphylococcus aureus* immediately after subculturing the skin, and all gave good growths. Our conclusion, therefore, is that sufficient metaphen may be carried over on the swabs to inhibit the growth of living but devitalized bacteria from the skin carried over at the same time but insufficient for inhibiting the growth of 4 mm. loopfuls of fresh vital twenty-four hour broth cultures of *Staphylococcus aureus*.

CONCLUSIONS

1. The application of 1:500 aqueous solution of metaphen to the skin for five minutes was found to be a highly efficient disinfectant.
2. In confirmation of the report of Raiziss, Severac and Moetsch, the application of 1:500 aqueous solution of metaphen for five minutes to the disinfected skin of rabbits secondarily contaminated with broth

cultures of various organisms usually resulted in complete disinfection, probably because the bacteria were on the surface of the skin.

3. The application of 1:500 aqueous solution of metaphen to the unprepared skin of human beings for five minutes resulted in complete disinfection in at least from 70 to 75 per cent of persons. In the remaining 25 to 30 per cent, disinfection was incomplete, probably because of a failure of the disinfectant in aqueous solution to reach and destroy organisms located in the depths of the skin in the time allowed. Metaphen solutions in alcohol and acetone were not tested.

4. In 95 per cent of cases, however, the application of 1:500 aqueous solution of metaphen to unprepared skins for five minutes resulted in the complete destruction of staphylococci, which are of most importance from the standpoint of disinfection in relation to surgery.

5. The degree of bacterial contamination of the skin influenced the degree of disinfectant activity of aqueous solutions of metaphen.

6. Subcultures of the skin with swabs into 10 cc. of broth, following the application of 1:500 aqueous solutions of metaphen, were always positive when inoculated with staphylococci and failed to corroborate the observations of White and Hill in these respects.

7. However, subcultures of the skin with swabs in 10 cc. of broth, following the application of 1:500 aqueous solutions of metaphen, apparently transfer sufficient of the compound to prove bacteriostatic for devitalized organisms.

8. Therefore, in tests of the bactericidal activity of metaphen on the skin, subcultures should be made in 100 cc. or larger volumes of broth, as advised by White and Hill.

THE DISCHARGE OF BILE INTO THE DUODENUM

AN EXPERIMENTAL STUDY *

CHARLES B. PUESTOW, M.D.

Fellow in Surgery, the Mayo Foundation

ROCHESTER, MINN.

The mechanism of biliary secretion and flow has been studied extensively for many years, yet some phases of it are not fully understood. This is due in part to the differences of opinion regarding the anatomy of this region and also to the difficulty of securing convincing experimental information without interfering with normal physiologic processes. The liver normally secretes bile continuously, although the rate is variable. The flow from the common bile duct into the duodenum, however, is interrupted. Most anatomic studies have shown the presence of a muscular arrangement at the duodenal end of the choledochus, which could act as a sphincter, and many physiologic experiments and hypotheses concerning a sphincter mechanism of the choledochus have been made. The studies have not all been concordant. The object of the present experimental study was to observe directly the flow of bile into the duodenum in the intact animal and thus attempt to determine the mechanism controlling the discharge of bile. Most previous direct observations of this mechanism have been made as acute experiments on anesthetized animals. Under such circumstances normal physiologic processes are likely to be disturbed. To eliminate such complicating factors, an operative procedure was devised that so exposed the duodenal orifice of the duct as to permit long and varied observations under different physiologic conditions in intact animals. Animals thus prepared remained in a seemingly normal condition for many weeks or months after operation. The anatomic derangement may have made some physiologic changes, for which, of course, allowance must be made. The experiments were concerned only with the direct observation of the duodenal orifice of the duct, its action and the flow of bile from it and with notation of the influences of other normal physiologic processes and of various substances administered orally and subcutaneously and applied locally to the exposed duodenal segment. After the satisfactory termination of these observations, cholecystectomy was performed, and the effects were noted.

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In 1861, Glisson¹ first intimated the existence of a sphincter at the duodenal end of the choledochus. Such a structure in man and in many animals has been carefully studied by Gage,² Oddi,³ Hendrickson,⁴ Letulle and Nattan-Larrier,⁵ Helly,⁶ Rost,⁷ Job⁸ and others. Doyon⁹ and Freeze¹⁰ concluded that the great splanchnic nerves contain the motor fibers to the biliary tract. Contrary to this opinion, Courtade and Guyon,¹¹ Bainbridge and Dale,¹² Lieb and McWhorter¹³ and Mann¹⁴ considered the vagi to be the motor nerves to the biliary passages. A theory of contrary innervation, causing simultaneous contraction of the gallbladder and dilatation of the orifice of the choledochus, has been advanced at various times by Foster¹⁵ and Doyon and

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2. Gage, S. H.: The Ampulla of Vater and the Pancreatic Ducts in the Domestic Cat, *Am. Quart. Micro. J.* **1**:123 and 169, 1879.

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6. Helly, K. K.: Die Schliessmuskulatur an den Mündungen des Gallen- und der Pankreasgänge, *Arch. f. mikr. Anat.* **54**:614, 1899.

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10. Freeze, J. A.: The Force of Contraction of the Gall-Bladder and the Course of Its Motor and Inhibitory Nerve Fibers, *Bull. Johns Hopkins Hosp.* **16**:235 (June) 1905.

11. Courtade, D., and Guyon, J. F.: Action motrice du pneumogastrique sur la vésicule biliaire, *Compt. rend. Soc. de biol.* **56**:313 (Feb. 20) 1904; Trajet des nerfs extrinsèques de la vésicule biliaire, *ibid.* **57**:874 (May 28) 1904.

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Meltzer¹⁶ and further supported by McMaster and Elman.¹⁷ On the other hand, the experiments and observations of Winkelstein and Aschner,¹⁸ Burget,¹⁹ Chiray and Pavel,²⁰ Whitaker²¹ and Berg²² have led them to conclude that contrary innervation does not control the flow of bile into the duodenum, or at least it is not an important factor.

Nearly all observers agree that a constricting force is effective at times in closing the duodenal end of the common bile duct. Many believe this to be the action of an independent sphincter. Some observers²³ believe that the tonus of the duodenal musculature is an important, if not the most important, element of resistance. Numerous experiments have shown that the sphincter in animals possessing a gallbladder will withstand a pressure equal to that of a column of water from 100 to 625 mm. in height. Many factors influence the tonus of the sphincter. Removal of the gallbladder, feeding of the animal and the application of acids and certain drugs to the duodenum tend to reduce it, while fasting the animals and the application of alkalis to the duodenum tend to raise it.

Various methods have been used to study the sphincter action at the duodenal end of the choledochus and its relation to the flow of

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bile. The duodenum of anesthetized animals has been incised opposite the papilla so as to expose the papillary orifice, and various experiments have then been performed. Rost inserted a cannula into the duodenum of dogs and thus studied the flow of bile into it before and after cholecystectomy. The studies here presented substantiate many of his observations. A cannula has been inserted into the common bile duct toward the duodenum and the sphincteric action studied by the resistance offered; duodenal tubes have been inserted in order to detect the presence or absence of flow of bile; the sphincters have been abolished in some animals, and the reactions of such animals have been compared with those of animals with intact sphincters. McWhorter,²⁴ by cutting the distal mucosa, and Burget, by severing and transplanting the distal end of the duct, did not note any effect on resistance of the sphincter; however, this resistance had been lowered by laying the duodenal portion of the duct wide open.²⁵ Burget cocaine-ized the orifice of the duct to eliminate any action of the sphincter that there might be, and noted the resistance then offered at the duodenal end of the duct and the effects of various drugs on it. He concluded that the function of the duodenal sphincter had been overemphasized, and that duodenal tonicity and peristalsis are significant in the regulation of the flow of bile.

The chief functions of the sphincteric action at the duodenal end of the choledochus are generally agreed to be: regulating the flow of bile into the duodenum, preventing back flow from the intestine into the duct and serving as a factor in the filling of the gallbladder.²⁶ Respiration, peristalsis and activity of the gallbladder have also been considered significant in the discharge of bile into the duodenum. Effects of various foods and drugs on the flow of bile have been studied extensively. Pavlov²⁷ noted that the administration of fat, meat extractives and gastric digestive products of white of egg was followed by a free flow of bile. Boyden²⁸ noted the emptying of the gallbladder

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after a meal of fats and believed the regulatory action of the sphincter to be important. Many observers have noted that the passage of acid chyme into the duodenum or the application of dilute hydrochloric acid to the region of the papilla produces flow of bile into the duodenum. An extensive survey of the literature and some personal observations on the anatomy and physiology of the duodenal end of the choledochus were reported by Giordano and Mann.²⁹

METHODS OF EXPERIMENTS

All operative procedures were carried out on dogs under ether anesthesia and with aseptic technic. The object of the surgical operations was to expose an isolated segment of duodenum containing the intramural portion and orifice of the

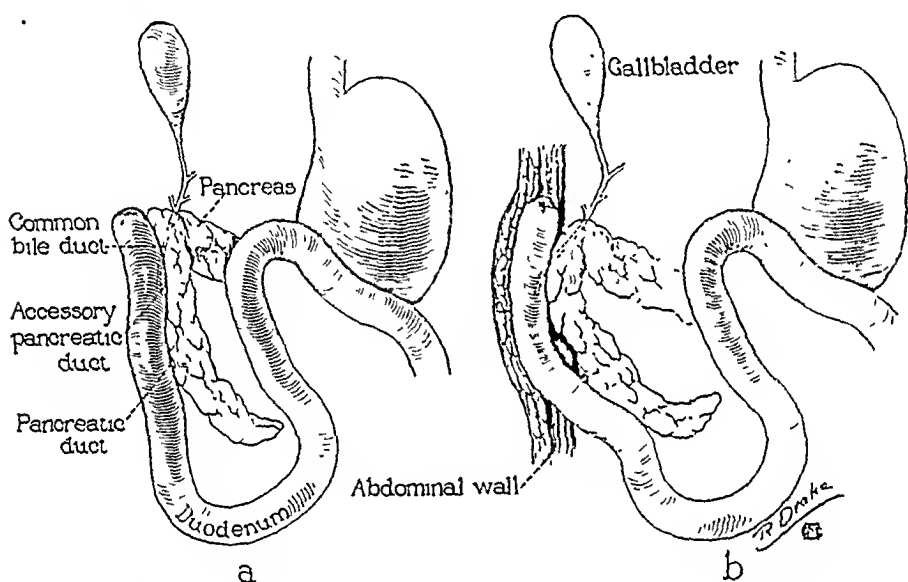


Fig. 1.—First (a) and second (b) stages of the operation.

choledochus in such a manner that the discharge of bile into the duodenum and the phenomena taking place at the orifice of the ampulla of Vater could be observed directly in intact animals. The intestinal tract was so rearranged that its content did not come in contact with the isolated segment of duodenum. The main pancreatic duct continued to empty into the intestine. Various procedures were employed to accomplish this, but it was found that the best results could be obtained by a three-stage operation, the technic of which is as follows:

First Stage (Fig. 1, a).—In this stage the pylorus is divided, the duodenal end is closed, and the upper part of the jejunum is united to the stomach. To accomplish this, either an anterior Polya operation may be employed, or after section of the pylorus and closure of both ends, gastrojejunostomy may be performed. Several weeks are allowed to elapse for the animal to recover fully.

Second Stage (Fig. 1, b).—The abdomen is again opened in the median line. The lesser pancreatic duct is isolated, cut close to the duodenum and evulsed. As

29. Giordano, A. S., and Mann, F. C.: The Sphincter of the Choledochus, Arch. Path. 4:943 (Dec.) 1927.

this duct opens into the duodenum with or close to the orifice of the choledochus, it is destroyed to eliminate any complicating factors that pancreatic secretion might produce in later observations. The pancreas is separated from the duodenum for a slight distance proximal and distal to the entrance of the choledochus into the bowel, and the abdominal muscle and layers of fascia are closed through these openings under the duodenum. The skin is closed over the duodenal segment, and the animal is allowed to recover.

Third Stage (Fig. 2).—The skin is incised over the bulging duodenal segment and dissected from it. The duodenum is opened longitudinally opposite the orifice of the choledochus. The papilla of Vater and that of the main pancreatic duct are located, and the duodenum is divided midway between them. The distal end of the duodenum is closed, care being taken not to obstruct the main pancreatic duct. The edges of skin are trimmed away from the remaining duodenal segment.

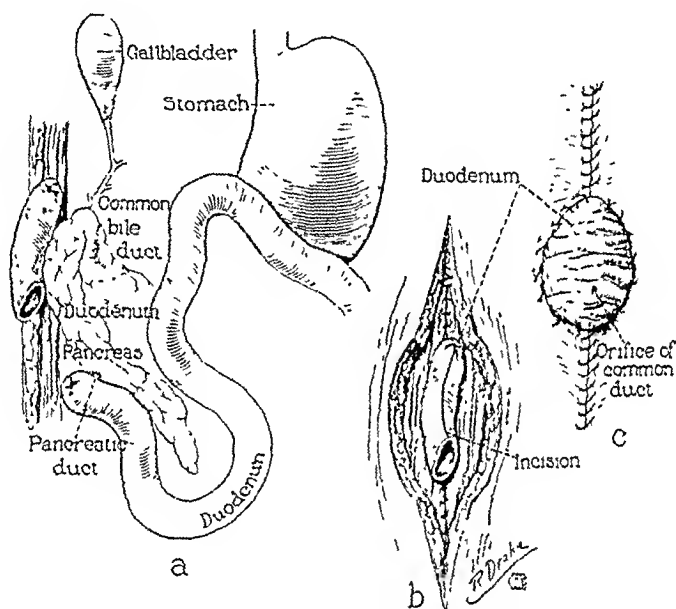


Fig. 2.—Third stage of operation: *a*, division of the duodenum between the papilla of Vater and the main pancreatic papilla; *b*, an isolated duodenal segment, showing the line of incision, and *c*, operation completed; the edges of the duodenal segment were sutured to the surrounding skin.

This segment, which contains the intramural portion and orifice of the choledochus, has already been opened. Its edges are sutured to the surrounding skin. If sufficient care is used in this stage of the operation, the peritoneal cavity need not be entered.

Observations were usually started several days after the completion of the operative procedures. The experiments were concerned only with direct observations of the exposed duodenal segment, the orifice of the choledochus and the flow of bile from it. Studies were made with the animals in fasting and in non-fasting states, and the effects of substances administered orally and subcutaneously and applied locally to the exposed duodenal segment were noted.

After the animals had thoroughly recovered from the third stage of the operation and had been observed for a length of time sufficient to obtain convincing data, the gallbladder was removed. This was done through a high left rectus

incision, the exposed portion of the duodenum and the choledochus being disturbed as little as possible. After recovery from this operation, similar studies were made to determine the effects of cholecystectomy.

RESULTS OF EXPERIMENTS

Observations on the series of animals that had a segment of duodenum containing the orifice of the choledochus exposed on the abdominal wall revealed certain constant physiologic phenomena. These will first be considered under various conditions in animals with the gallbladder intact.

After a fast of twelve hours or longer bile did not flow from the orifice of the choledochus during hours of observation. This was constant in all but two animals observed. Later exploration in one of these revealed a diseased gallbladder and a markedly dilated choledochus. In the other animal bile did not flow in the fasting state in early observations but later, particularly after catheterization of the choledochus, there was a moderate flow, at times, of yellow bile. One or two other animals occasionally expressed a drop of bile during violent muscular straining, but none was noted at any other time. The orifice of the choledochus was usually closed in the fasting state. However, this was not a constant observation. Frequently when the exposed duodenum contracted, the orifice dilated to varying degrees and gradually closed again. If the intestinal segment was very active, the ampulla would frequently remain open. On a few occasions visible dilatation occurred when intestinal activity was not observed.

The exposed segment of duodenum usually showed very little activity when the animal was deprived of food. At times mild contractions were visible; strong contractions seldom occurred. Often fairly long periods would elapse without visible activity. On a few occasions, when there was audible borborygmus, the exposed segment became more active. The mucosa was usually pallid or only slightly hyperemic. The amount of duodenal secretion was not great. By passing a catheter attached to a manometer through the orifice of the duct into the choledochus, the intraductal pressure was found to be from 140 to 170 mm. of bile.

Feeding produced marked and constant changes. There was almost invariably a flow of bile from the orifice of the choledochus. The bile was usually dark brown and viscid. Generally an initial flow occurred either at the sight and smell of food or during its ingestion. The bile oozed steadily and profusely for from one to three or four minutes and then the flow ceased partially or completely for from ten to twenty minutes. During that time, there was little duodenal activity.

A secondary profuse flow of dark brown, viscid bile began from ten to twenty minutes after feeding. It usually occurred as steady oozing which lasted from a few to fifteen minutes. The flow then occurred in brief oozes and spurts, gradually diminishing in amount and frequency after the first half to one hour and generally almost completely ceasing after from three to four hours. The bile gradually became lighter in color and less viscid. Occasionally the primary flow continued without interruption. On some occasions, the flow did not occur until from fifteen to thirty minutes after feeding, when it began and continued for several hours.

The relationship of other physiologic processes to flow of bile after feeding was studied. Immediately after operation and for the following week or ten days, spurts of bile were definitely related to respirations. Series of from two to twelve spurts would occur on successive respirations, with intervals of several minutes between such series. Deep inspirations were accompanied by large outpourings of bile. Gradually, as the duodenal segment recovered its tonus and activity, spurts of bile became less related to respiration and finally seemed to be scarcely influenced by it.

During the first week or ten days after operation, the exposed duodenal segment did not show visible activity. Gradually it regained its tonus and activity, and attained maximal recovery from two to three weeks after operation. After this time it was fairly consistent in its reactions. As has been noted, it showed little activity in the fasting state. Feeding sometimes produced an immediate increase of contractions for a few minutes, but generally it did not. During the first ten to twenty minutes after feeding, there was little visible change. During this time, bile usually oozed steadily; then the segment became more hyperemic and gradually increased in tonus and activity. Soon definite peristaltic waves could be seen. These contractions usually increased the quantity of bile into accompanying spurts. The amount of duodenal activity gradually increased and reached a maximum about half an hour after feeding. The flow of bile became more interrupted, occurring chiefly in spurts; these frequently were associated with contractions. However, all duodenal contractions were not accompanied by spurts of bile. Sometimes a discharge of bile would occur when there were no duodenal activity and no other visible stimulus. After a peristaltic contraction, the segment of bowel sometimes appeared to relax; the orifice dilated, and bile would pour out for several seconds.

Muscular straining sometimes produced small spurts of bile. Mild muscular movements usually had no effect. Active stretching of the animal or straining sometimes caused bile to be discharged, but only after feeding.

Psychic factors appeared to have some effect on the flow of the bile. In the fasting state excitement did not promote flow. The smell of food sometimes caused considerable outpouring of bile, and the primary discharge of bile with feeding must have been of psychic or reflex origin, as it began often before the meal had reached the stomach. Excitement sometimes delayed or inhibited the flow of bile. On one occasion, an animal that regularly expressed bile after feeding showed no flow of bile for an hour after the meal. During this time, several strangers were observing the animal and appeared to disturb him. Five minutes after the strangers departed, the animal became quiet and bile flowed profusely.

After a meal the orifice of the choledochus was usually patent. It would dilate with the spurting of bile and would remain open if the duodenum was active and spurts of bile were frequent. When the flow of bile and duodenal contractions diminished or became more interrupted, the orifice closed partially but not completely.

These responses to feeding were the usual observations following a meal of egg yolk and cream. Lean horse meat produced a rather similar response with some variations. Frequently the initial flow did not begin until from fifteen to thirty minutes after feeding. The bile often appeared lighter in color and less viscid than after a meal of fat. The flow of bile usually lasted longer after a meal of meat, and the quantity of hepatic bile was greater. Skimmed milk was followed by a flow of bile similar to that produced by lean meat. The effects of various types of foods on duodenal activity appeared to be the same. Water administered by mouth stimulated the exposed duodenum to increased activity, but did not produce a flow of bile. A saturated solution of magnesium sulphate administered by mouth was followed by violent contractions of the exposed duodenum and active purgation of the animal, but bile was not expressed. A meal of fat administered three hours later was followed by an immediate flow of brown, viscid bile.

After standardizing the responses of animals to various conditions and test substances, cholecystectomy was performed. Removal of the gallbladder was followed by definite changes in the flow of bile. In the fasting animal there was a constant flow. The bile was usually light in color and watery, but became somewhat darker, thicker and more scant as the fast was prolonged. It flowed in spurts and brief oozes associated with many factors. Respirations, especially if deep, often were associated with spurts of bile. Slight muscular effort produced similar results. Active stretching of the animal often was accompanied by considerable outpouring of bile. Duodenal contractions were also contributory causes of spurts of bile but were not significant

in the fasting state because the exposed segment showed little activity. The orifice of the choledochus was almost constantly patent. Feeding had the same effect on the exposed duodenum after cholecystectomy as with the gallbladder intact; that is, it produced a gradual increase of activity, secretion and hyperemia. It had very little effect on the flow of bile. There was no initial or subsequent outpouring of brown bile. For the first half hour the flow appeared similar to that before feeding, except that as the duodenal segment became more active spurts of bile became more related to this activity. However, there did not seem to be as close a relationship between peristalsis and spurts of bile after removal of the gallbladder as before it. The amount of bile gradually increased, and the color became somewhat lighter after a meal of lean meat. This was true to a much smaller degree after a meal of fat.

The intraductal pressure in the choledochus of the fasting animal after cholecystectomy was greatly reduced. Twenty-four hours after operation the pressure was found to be only from 20 to 30 mm. of bile. Subsequent readings showed a slight rise of pressure, but readings taken several months after cholecystectomy were never higher than 60 mm. of bile.

Various solutions were poured over the exposed segment of duodenum and the papilla of Vater in an effort to elicit any effects of local stimulation. The temperatures were varied, but this seemed to make little difference. Most solutions were used at body temperature. The following results were noted. Distilled water usually had no effect, though occasionally it stimulated duodenal contractions. Physiologic solution of sodium chloride acted similarly, but seemed to excite duodenal contractions more frequently. A solution of 25 per cent magnesium sulphate had an inconstant stimulating effect on the activity of the duodenal musculature but no evident independent action on the orifice of the choledochus. Usually bile did not flow after its use, but occasionally there were a few spurts of yellow bile. Dilute hydrochloric acid seemed to have a more constant stimulating effect on duodenal contractions, and its use was followed more frequently by small spurts of yellow bile. Alkalis in the form of dilute sodium hydroxide and sodium bicarbonate had no visible effect on the duodenum or orifice and did not promote flow of bile. Mechanical stimulation in the form of sponging was followed by contraction of the duodenal segment and orifice of the choledochus but never by the discharge of bile. The intravenous administration of bile salts was followed in half an hour by a profuse flow of light yellow, watery bile which lasted more than three hours (figs. 3 to 6).

COMMENT

It is difficult to determine what effect the anatomic sectioning and reconstruction, as performed in these experiments, had on the innervation and function of the extrahepatic biliary tract and the isolated



Fig. 3.—Animal in fasting state. The orifice of the choledochus is patent, but there is no flow of bile.



Fig. 4.—Same animal as in figure 3, fifteen minutes after the meal of fat. Dark brown bile is flowing profusely from the orifice of the choledochus.

segment of duodenum. Most of the vagal branches of this region were divided, but the sympathetic nerves that follow the hepatic artery were left intact. However, as apparently normal activity returned to the exposed segment of bowel and as the flow of bile responded to stimuli in what is thought to be a normal manner, it seems justifiable

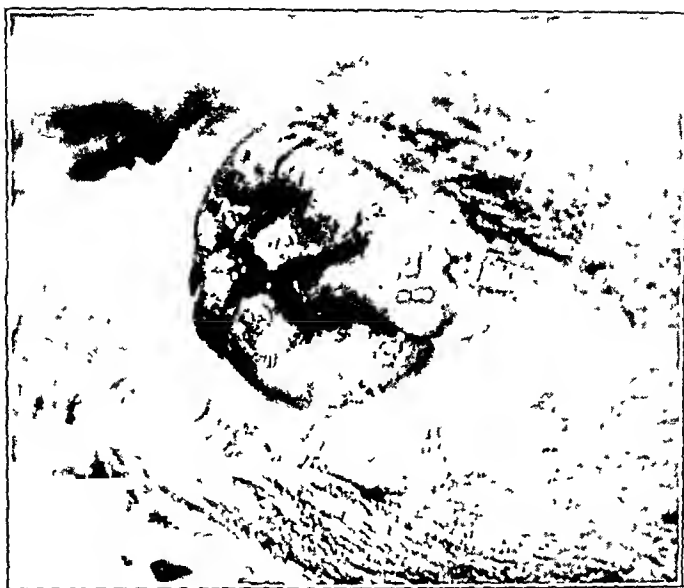


Fig 5.—Exposed segment of duodenum. Animal in fasting state. The segment is relaxed, and there is no flow of bile.



Fig. 6.—Same animal as in figure 5, after a meal of fat. The duodenal segment shows an increased tonus, and bile is flowing from the orifice.

to assume that normal physiologic processes were not greatly disturbed. By this method of study the effects of anesthesia and the immediate effects of operative trauma could be avoided. Subsequent observations showed the significance of this, as responses soon after operation were different from those obtained when the animal had completely recovered from the operative procedures. The animals were trained to lie quietly on the table for hours at a time, and their normal responses were well established before each test substance was given or observation procedure carried out. The observations on the various animals in this series agreed with and confirmed those made on the other members of the series.

It was found that bile did not flow from the orifice of the choledochus in the fasting animal with an intact normal gallbladder. An animal in which bile flowed in the fasting state was found to have a diseased gallbladder and a markedly dilated choledochus. Another animal responded normally at first, but later, after the orifice of the duct had been traumatized, some bile flowed when the animal was fasting. Later, however, bile again ceased to flow in the fasting state, suggesting that the regulatory mechanism was temporarily disturbed. The absence of the discharge of bile in the fasting state must be due to one of two factors: Either there are insufficient bile and bile pressure in the choledochus to cause a flow of bile from the orifice, or there is a sphincter mechanism at the duodenal end of the choledochus preventing the discharge of bile. Various observers have shown that the first of these could not be the cause. With a T-tube in the common bile duct, Potter and Mann³⁰ found an average intraductal pressure of 95 mm. of bile. McMaster and Elman sectioned the choledochus in animals that had been deprived of food and found that the pressure at the proximal end rose to from 100 to 150 mm. of bile. Nuboer³¹ determined that the pressure in the choledochus in fasting dogs was from 90 to 100 mm. of water. In the series here presented, animals in a fasting state were found to have an intraductal pressure in the choledochus of from 140 to 170 mm. of bile. When the manometer was turned down and the bile was allowed to flow out, a considerable quantity was obtained. These experiments suggest that there is sufficient pressure in the choledochus in fasting animals to induce flow of bile from the orifice if the flow is not prevented by a sphincter mechanism. Is this sphincter action produced by duodenal tonus and

30. Potter, J. C., and Mann, F. C.: Pressure Changes in the Biliary Tract, *Am. J. M. Sc.* **171**:202 (Feb.) 1926.

31. Nuboer, J. F.: Die Funktion des Oddischen Muskels, abstr. *Ber. ii. d. ges. Physiol.* **51**:81, 1929.

activity alone or does some other sphincter mechanism play a part? There are several factors that argue against the former contention. The flow of bile apparently is not dependent on duodenal activity alone because the smell of food may cause a flow of bile when visible change cannot be seen in the exposed segment. After the animal has been fed, the discharge of bile often occurs when the segment is quiet. Also in the fasting state the exposed segment may become very active without discharge of bile. This was noted especially after the oral administration of water and of magnesium sulphate solution. These observations suggest a special sphincter mechanism. Many anatomic studies have been made of the duodenal portion of the choledochus, and arrangements of muscles that could act as a sphincter have been described as being around the orifice of the duct and around the portion of the duct that traverses the duodenal musculature. Hendrickson described a complete muscle ring around the end of the duct and just under the mucosa, which he believed constituted the sphincter of the common bile duct. It does not seem likely that this alone constitutes the sphincter, because frequently in the fasting animal the orifice of the duct was widely dilated and the lumen of the duct was visibly open for several millimeters but bile did not flow. There is apparently a sphincter mechanism in the intramural portion of the choledochus which is not entirely dependent on duodenal tonus and activity.

In these experiments it was found that feeding was followed by a flow of bile. There was usually a primary flow of brief duration. This was not a result of stimulation due to absorption of food because the flow often began when the animal sighted and smelled the food, but before it had ingested any of it. At other times the flow began with the beginning of ingestion of food, before the substance had had time to reach the stomach. The primary flow was evidently a reflex response to psychic stimulation. The initial flow usually lasted only from one to three minutes and occurred as a profuse steady ooze. The flow usually diminished or ceased during the next ten to thirty minutes. The secondary flow then began and continued for several hours. It began after some of the food had had time to be absorbed. Bile flowed first in prolonged oozes which gradually became of shorter duration and were largely replaced by spurts. Several factors were associated with the spurting of bile. The most significant of these appeared to be duodenal activity. As the duodenum gradually became more active after feeding, spurts of bile frequently accompanied its contractions. Sometimes after a contraction the exposed segment of duodenum relaxed and bile flowed for a few seconds. However, all spurts of bile were not associated with visible duodenal activity. Respi-

ration was definitely related to spurts of bile soon after operation, before the exposed duodenum had recovered its tonus and activity. After the effects of operative trauma had disappeared and the exposed bowel was healed and active, respiration had little effect on the discharge of bile. Contractions of the abdominal musculature were occasionally accompanied by spurts of bile, but this accounted for only a small percentage of the bile discharged. Excitement often seemed to have an inhibitory influence on the discharge of bile. Spurts of bile were occasionally observed independent of any visible factors, and suggested the possibility of contraction of the gallbladder as a cause. This was not proved.

The type of food administered had some effect on the responding flow of bile. Both fats and lean meat produced a flow, but the former often called forth a prompter flow, and the bile was frequently darker and more viscid. However, the flow after fats did not last as long as after lean meat. The latter did not produce so profuse an immediate flow, but the total quantity was larger, the flow lasted longer, and the bile was of a more hepatic type, especially after the first half hour.

Cholecystectomy had a definite and constant effect on the flow of bile from the duodenal end of the choledochus. There was always a flow in the fasting state. This occurred chiefly in spurts accompanying slight activities, such as respiration, duodenal contractions or movements of the animal. Frequently spurts occurred independent of any visible stimulus. They were not forceful, and the bile did not seem to be under tension. The orifice of the choledochus was almost always open. The intraductal pressure in the choledochus was very low, from 10 to 20 mm. of bile, soon after operation. This was found to be the case within twenty-four hours of operation. It has been supposed that the loss of sphincter action following cholecystectomy was due to an overpowering and paralyzing action of the secretory pressure of the liver on the muscle after the concentrating activity of the gallbladder had been removed. It hardly seems likely that the sphincter could be paralyzed as soon after cholecystectomy as occurred in these experiments, and a possible reflex loss of tonus is suggested.

Foods did not alter the flow of bile immediately after cholecystectomy. The quantity of bile slowly increased after feeding, suggesting stimulation of hepatic secretion. The bile became less viscid and lighter yellow. As the duodenum responded to food and became more active it influenced the discharge of bile to a greater extent than before feeding, but less than it did before cholecystectomy.

Various solutions applied to the exposed segment had little effect. They sometimes caused a slight increase of duodenal activity and occasionally a spurt of bile. The responses did not vary sufficiently

with different test substances to permit any definite deductions. As only a small portion of duodenum was exposed in these animals, it would not be fair to draw conclusions regarding the effects of these substances on the entire duodenum. However, it seemed evident that they had little direct effect on the orifice of the choledochus.

An interesting observation was made on the effect of fasting and feeding on duodenal activity. The isolated segment of bowel was relatively inactive in the fasting state and became definitely more active after feeding. There was also an increase of hyperemia and an apparent increase of duodenal secretion. As food did not come in direct contact with the isolated bowel these responses could not have resulted from actual contact with food or distention of the segment and must have resulted from stimulation transmitted by either nervous or vascular routes.

SUMMARY

The object of this experimental investigation was to study some of the factors concerned in the physiology of flow of bile into the duodenum. Operative procedures were devised that provided animal subjects with an isolated segment of duodenum exposed on the abdominal wall. This segment of bowel was opened longitudinally and sutured to the surrounding skin. It contained the orifice and the intramural portion of the choledochus. The accessory pancreatic duct was evulsed to avoid any complicating factors that it might produce. As the exposed duodenum was isolated from the remainder of the bowel, the intestinal contents did not come in contact with it. These animals lived for months in an apparently normal condition and permitted observations uncomplicated by the effects of anesthesia and the immediate effects of operative trauma. Studies were made with the animals in fasting and in nonfasting states. The effects of various test substances administered orally, intravenously and locally to the exposed segment of duodenum were determined. After completing these observations, the gallbladder was removed and similar studies were repeated to determine the influence of cholecystectomy.

The following observations and deductions were made: In the fasting animal with an intact normal gallbladder, the orifice of the choledochus was usually closed, the exposed duodenal segment was relatively inactive, and there was almost never flow of bile. The intraductal pressure in the choledochus was found to be from 140 to 170 mm. of bile. The absence of flow of bile was evidently due to a sphincter mechanism at the duodenal end of the choledochus. The tonus of the duodenal musculature apparently was not the sole cause of the sphincter action, and a special sphincter mechanism was suggested.

Food stimulated flow of brown viscid bile. There was usually an initial ooze beginning with the ingestion of food and lasting for from one to three minutes. This was apparently due to psychic or reflex stimulation. A secondary flow began from ten to thirty minutes later and lasted several hours. The bile flowed in brief oozes and spurts, which were frequently related to activity of the exposed duodenum but often occurred independently. Respiration was not a significant factor in the discharge of bile. The exposed segment of bowel became more active and more hyperemic after feeding and reached a maximal degree of peristalsis about half an hour after the ingestion of food.

After cholecystectomy, bile continued to flow in the fasting as well as in the nonfasting state. It was lighter in color and less viscid than the bile that flowed after an animal with an intact normal gallbladder had been fed. Feeding had little effect on the discharge of bile other than to increase the quantity slightly. The orifice of the choledochus was constantly patent. Duodenal activity and its response to feeding were not influenced by cholecystectomy. After removal of the gallbladder, the intraductal pressure in the choledochus of the fasting animal was reduced to from 10 to 20 mm. of bile.

Bile salts administered intravenously produced a profuse flow of thin yellow bile. Solutions applied locally to the exposed segment of duodenum occasionally stimulated a slight degree of duodenal activity and rarely were followed by the expulsion of a drop of bile, but generally they did not produce a definite response.

SPONTANEOUS PEPTIC ULCERS OF DUODENUM AFTER CONTINUED LOSS OF TOTAL PANCREATIC JUICE *

ROBERT ELMAN, M.D.

AND

A. F. HARTMANN, M.D.

ST. LOUIS

In a previous paper¹ from this laboratory mention was made of the finding of peptic ulcerations of the duodenum just distal to the pylorus in a dog that lost the entire external secretion of the pancreas and was kept alive and in good condition for two weeks with daily intraperitoneal injections of Ringer's solution. This observation was so striking and so unexpected that a number of other dogs were subjected to the same experimental procedure. Duodenal ulcers were found in every case. This finding, as will be pointed out, is not surprising after all and seems to fit in with a number of related observations by others.

PREVIOUS WORK

Most of the tremendous amount of work that has been done on experimental peptic ulcers has dealt with those on the gastric side of the pylorus. These observations have been successively reviewed by many authors. MacCallum,² in 1904, reviewed most of the earlier experiments that were largely concerned with the production of mucosal defects in a variety of ways. In a book by Rost³ most of the literature up to 1921 has been analyzed. More important, however, than the actual production of a lesion is the study of the factors that keep it from healing, and hence, lead to chronicity. Thus, it has been repeatedly shown that the mucous membrane of the stomach has a remarkable regenerative power so that the removal of large areas of mucosa is rapidly followed, usually within two weeks, by complete healing. There is also abundant clinical evidence to show that duodenal ulcers are also prone to heal spontaneously only to recur and heal again under a variety

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* From the Departments of Surgery and of Pediatrics, Washington University School of Medicine, and Barnes and St. Louis Children's Hospitals.

1. Elman, R., and Hartmann, A. F.: Cause of Death Following Rapidly Total Loss of Pancreatic Juice, *Arch. Surg.* **20**:333 (Feb.) 1930.

2. MacCallum, W. G.: *Am. Med.* **8**:452, 1904.

3. Rost, F.: *Pathologische Physiologie des Chirurgen*, ed. 2, Leipzig, F. C. W. Vogel, 1921, p. 102.

of circumstances. Many such cases have been followed by fluoroscopic and by roentgenologic examinations. It is probable, indeed, that much of the dispute and disagreement as to the results following various modes of treatment is explainable on this basis. Whatever the primary cause of peptic ulceration, whether it is vascular, neurogenic, bacterial or traumatic, the factors promoting its chronicity would seem to be of most practical and theoretical importance. Prominent among these factors are high acidity and roughness of the gastric contents. Rost³ as well as McCann⁴ summarized most of this work in some detail. High acidity will be discussed later. It should be emphasized here that experimental work done with dogs is probably of greater significance than that performed on other animals. Dogs are particularly suited for the study of duodenal ulcers since this lesion practically never occurs normally, as shown by a study of 1,000 routine autopsies on dogs reported by Ivy.⁵

In this paper we are concerned specifically with the observations of spontaneous duodenal ulcerations noted during the course of experiments in which the total pancreatic juice was drained to the outside. A number of observations by other workers fit in with the present experiments. Most important, perhaps, are ulcers noted by Mann and Williamson⁶ which also occurred just distal to the pylorus in dogs and which developed following diversion of the entire duodenal contents. This was achieved by an operation they termed "surgical drainage of the duodenum." By this procedure the entire contents of the duodenum were made to empty low down by resecting it, closing one end and suturing the other end into the terminal ileum. The pylorus and the jejunum were then anastomosed end-to-end. Peptic ulcers, some perforating, were noted just distal to this line of suture in fourteen of sixteen dogs. They were explained by the assumption that diversion of the alkaline duodenal contents permitted the acid gastric juice to attack and ulcerate the jejunal mucosa. These observations have been abundantly confirmed first by Morton⁷ in all of eighteen dogs and recently by Weiss⁸ and also by Dragstedt.⁹ It is of special interest that Morton noted that "duodenal drainage" prevented healing and resulted in chronicity of experimental mucosal defects in the stomach in 50 per cent of his animals.

4. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* **19**:600 (Oct.) 1929.

5. Ivy, A. C.: Physiology of the Stomach: Studies on Gastric Ulcer, *Arch. Int. Med.* **25**:6 (Jan.) 1920.

6. Mann, F. C., and Williamson, C. S.: *Ann. Surg.* **77**:409, 1923.

7. Morton, C. B.: *Ann. Surg.* **85**:207, 1927.

8. Weiss, A. A., and Gurriaran, G.: *Bull. et mém. Soc. nat. de chir.* **56**:8, 1930.

9. Dragstedt, L. R.: Personal communication.

In many other analogous experiments peptic ulcers at the exit of the stomach have been described which also have an important bearing on the present findings since they concern drainage of alkaline duodenal contents or interference with their normal behavior. Thus Grey¹⁰ noted during the course of transplantation experiments in two dogs that peptic ulcerations of the duodenum occurred after pancreatic and bile ducts were made to empty in the terminal ileum. Mann and Williamson⁶ also performed this experiment on a large number of dogs, thirty of which survived eight days or longer; duodenal ulcers were found in ten. Bickel,¹¹ in 1909, extirpated the duodenum in a dog, transplanted the bile and pancreatic ducts into the abdominal wall and reestablished intestinal continuity by a gastro-enterostomy. After four and one-half weeks, the animal died. Peritonitis from a perforating ulcer of the jejunum at the stoma was found at autopsy.

Similar experiments were reported by Exalto¹² in 1911. He noted that jejunal ulcerations were always present at the stoma of an experimental gastro-jejunostomy provided the duodenum was transplanted so as to empty its contents low in the gastro-intestinal tract. Baggio,¹³ an Italian surgeon, has recently found similar ulcerations just distal to the emptying point of the stomach in four of six dogs subjected to a gastric resection by a "Y-anastomosis of Roux," an operation in which the gastric juice pours directly over the unprotected jejunal mucosa, the duodenal contents draining a little lower down. Dott and Lim¹⁴ reported that marginal ulcers were nearly always formed after an experimental gastro-enterostomy whenever the pylorus was occluded. This agrees with the clinical experience of von Haberer¹⁵ who found that jejunal ulcers developed in 12 of 71 cases with pyloric occlusion in which he performed a gastro-enterostomy, whereas they developed in only 3 of 275 cases without occlusion. The latter findings were assumed to be due to the fact that closing of the pylorus precluded duodenal reflux and hence the unneutralized gastric contents poured directly on the jejunal mucosa. Ordinarily this does not occur, since it is well known that whatever the modus operandi of a gastro-enterostomy in the absence of organic pyloric stenosis most of the gastric contents leave the stomach via the pylorus and not the stoma.³

10. Grey, E. G.: *Surg., Gynec. & Obst.* **28**:36, 1919.

11. Bickel, A.: *Berl. klin. Wchnschr.* **46**:1201, 1909.

12. Exalto, J.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **23**:13, 1911.

13. Baggio, G.: *Ann. ital. di chir.* **3**:583, 1924; abstr., *Surg., Gynec. & Obst.* **40**:26, 1925.

14. Dott, N. M., and Lim, R. K. S.: *Quart. J. Exper. Physiol., supp.*, 1923, p. 109.

15. von Haberer, H.: *Deutsche Ztschr. f. Chir.* **172**:1, 1922.

All of the experimenters thus far have explained these ulcers mainly on a chemical basis as due to the removal of or interference with the normal neutralizing effect of the alkaline duodenal secretions on gastric acidity. A dissenting opinion was recently voiced by McCann⁴ on the basis of his own experiments. He diverted the duodenal contents by the method of Mann and Williamson,⁶ but sutured the duodenum into the fundus of the stomach rather than into the terminal ileum. He studied the gastric acidity before and after the operation and found it unchanged. Ulcerations distal to the pylorus in his experiments, moreover, were just as frequent as when the duodenum was sutured into the terminal ileum. He inferred, therefore, that the neutralizing effect of the alkaline duodenal contents on gastric acidity had nothing to do with the formation of the ulcers and that mechanical rather than chemical factors were largely responsible for them. While the observations are clearcut and definite, the studies of gastric acidity, unfortunately, were made with a test meal of ground meat which, as is well known, combines so readily with hydrochloric acid as to mask to a considerable extent the actual acidity developed. Diametrically opposed findings, moreover, have been reported by Steinberg, Brougher and Vidgoff,¹⁶ who used a test meal of 300 cc. of water containing Liebig's extract of beef. These workers found a much higher acidity following "duodenal drainage" into the terminal ileum. That the high acidity was due to faulty neutralization was shown by their use of an "acid test meal" which was much more slowly and incompletely neutralized than normal. These workers also proved that the difference in acidity was not due to alterations in the secretory activity of the stomach, for the juice from a Pavlov pouch showed no alteration in its acid content. The finding of ulcers in the experiments of McCann, finally, may not be in disagreement with those already mentioned. Anastomosis of the resected duodenum to the stomach does not necessarily mean free and continuous drainage, for it seems not improbable that the depth and strength of gastric peristalsis would tend rather to drive gastric contents into the loop or at least seriously interfere with an effective flow of the duodenal contents into the stomach. Neutralization of gastric acidity by the alkaline pancreatic juice might thus be seriously interfered with and the experiment, indeed, be one analogous to those in which the duodenum is sutured into the terminal ileum.

Spontaneous duodenal ulcers of a similar nature and at the same site, i. e., just distal to the pylorus, were noted by Kapsinow¹⁷ in

16. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in Chemistry of the Contents of Stomach Following Gastric Operations, *Arch. Surg.* **15**:749 (Nov.) 1927.

17. Kapsinow, R.: *Ann. Surg.* **83**:614, 1926.

seventeen of forty-three dogs in which the total bile was diverted to the outside for two weeks or longer. Bile drainage was effected by anastomosis of the gallbladder to the right renal pelvis, followed by ligation of the common duct, so that the entire bile flowed into and was excreted from the urinary bladder on micturition. The dogs were in poor condition at autopsy, however, and it seems difficult to know just what part inanition played in the formation of the lesion. Similar ulcerations were described recently by Berg and Jobling¹⁸ in thirteen of twenty-three dogs in which the total bile was excluded from the duodenum by drainage to the outside, by total biliary obstruction or by drainage followed by obstruction. Some of their dogs showing ulcers at autopsy also had pneumonia. Their drainage experiments were performed by the closed collecting system first described by Rous and McMaster.¹⁹ In contrast to these findings are the original observations of the latter workers, who make no note as to the presence of duodenal ulcers. One of us (Dr. Elman) has observed a great many such dogs with bile fistulas, all kept in excellent physical condition, some for as long as four months, without noting such a lesion.

METHODS

The intubation of the main pancreatic duct in dogs so as to obtain the total external pancreatic secretion has been described in detail elsewhere.²⁰ By this technic the secretion was obtained under sterile conditions from the entire pancreas and for the entire twenty-four hours, as described in a previous paper. Such a loss of pancreatic juice soon leads to a fatal outcome.²⁰ In the present experiments life was maintained in spite of continued drainage by the daily administration of 500 cc. of "combined solution"²¹ in 5 per cent dextrose, intraperitoneally. Pancreatic juice was collected daily with aseptic precautions, and by culture or the examination of the sediment from a centrifugated specimen, the presence or absence of infection was ascertained. Whenever infection occurred, the animal was chloroformed and autopsy performed. Drainage was maintained for at least thirteen days in the present experiments. The animals were fed carefully, the average daily diet consisting of 500 cc. of milk, 200 Gm. of chopped lean meat, either cooked or raw, and several dog biscuits. The operations were all carried out under complete morphine-ether anesthesia. At the termination of the experiment the animals were killed with chloroform, and autopsy performed immediately. Frequent analyses of the main chemical constituents of the blood were made.

18. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, *Arch. Surg.* **20**:997 (June) 1930.

19. Rous, P., and McMaster, P. D.: *J. Exper. Med.* **37**:11, 1923.

20. Elman, R., and McCaughan, J. M.: *J. Exper. Med.* **45**:561, 1927.

21. Hartmann, A. F., and Elman, R.: *J. Exper. Med.* **50**:387, 1929.

RESULTS

One large ulcer was found just distal to the pylorus on the posterior or superior aspect of the duodenum in each of the six dogs studied. In some dogs one or two smaller ulcers were noted a few millimeters distally. The ulcers were generally round or oval, but in dog 235 (fig. 1) the edges were irregularly oval and in dog 12 (fig. 2) the ulcer was

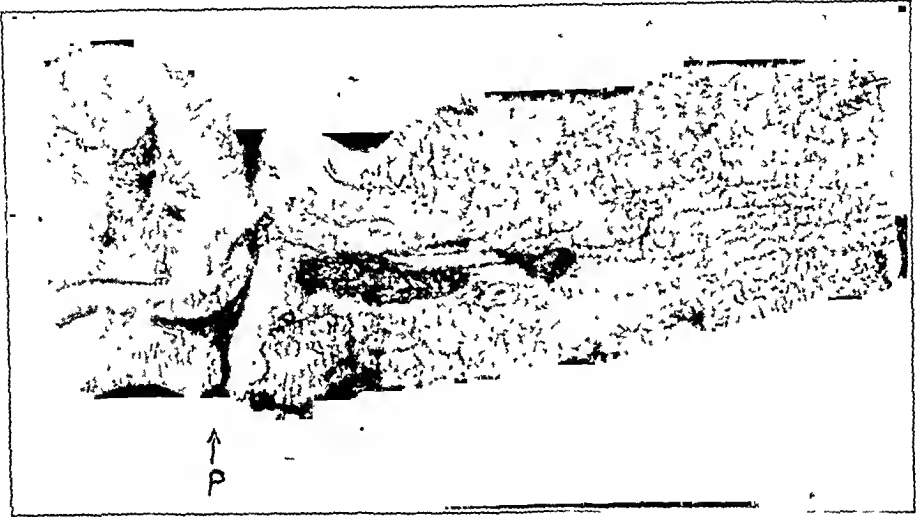


Fig. 1 (dog 235).—From a photograph of two ulcers just distal to the pylorus (P).



Fig. 2 (dog 12).—From a photograph of a single ulcer just distal to the pylorus (P).

semilunar. In several, blood clots were present over the lesion, but they could readily be removed. Bleeding was not infrequent, since streaks of blood were usually found in the jejunal contents at autopsy and often in the stools during life. Except possibly in dog 235 (fig. 3), no tendency to perforation was noted, which is not surprising in view of the relatively short duration of the experiments. On the other hand, no evidence of healing was seen. The microscopic study of the lesion

also did not show any sign of regeneration, the base extending down to the muscularis, which was edematous and frequently not even covered with granulation tissue. Figures 3, 4 and 5 were made from microscopic sections from three of these dogs. The table shows the amount of secretion collected and the duration of the experiments in each case. The stomach showed no abnormalities, nor were any other lesions found elsewhere. The peritoneum in each case was glistening, the operative wounds had healed and no evidence of infection in the pancreas or collecting system made out.



Fig. 3 (dog 235).—Sketch from a cross-section of a large ulcer, showing beginning penetration at one point (*P*).

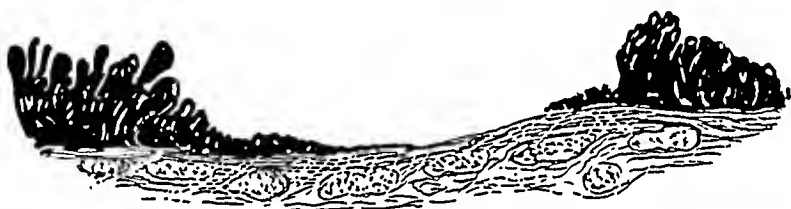


Fig. 4 (dog 12).—Sketch from a cross-section of a large ulcer showing absence of granulation and healing.

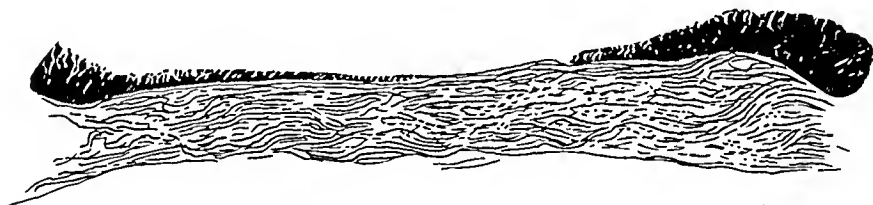


Fig. 5 (dog 23).—Sketch from a cross-section of a large ulcer. High magnification of this and other ulcers show signs of inflammatory reaction at the base.

It should be emphasized that the general condition of these dogs was good. They were killed in each case only because of accidental infection of the pancreatic juice, because the flow suddenly stopped, owing to a kink or other obstruction to the collecting system, or because it was deemed that sufficient time had elapsed to demonstrate the lesion. There was, it is true, definite and once marked loss of weight, but the dogs were lively, active, alert and ate fairly well despite certain evidences of gastric irritability already reported in previous papers.²² The food was

22. Elman and Hartmann (footnote 1). Elman and McCaughan (footnote 20).

taken, in general, more slowly than normally, and water and milk were lapped only at infrequent intervals and in small amounts. Dry dog biscuit was most relished, although meat was also eaten, some preferring it raw and others cooked. Vomiting sometimes occurred spontaneously. It was particularly apt to develop if milk or water was taken rapidly. If 300 cc. of milk was given by gavage, it would invariably be thrown up soon afterward. The chemical study of the blood showed little or no deviation from normal.

Though no special control animals were observed, it may be noted that in a great many previous experiments in which the pancreatic duct had been intubated for periods of one week or less, duodenal ulcers were never observed. Intraperitoneal solutions have also been injected into a great many dogs for a variety of reasons and ulcers never occurred in them.

Summary for Dogs with Duodenal Ulcer Draining the Total Pancreatic Juice

Dog	Weight, Kg.	Sex	Days of Drain- age	Average Output of Pancreatic Juice per 24 Hours, Cc.	Comment
11	10	F	14	364	Eats only cooked meat and biscuits
235	13	M	15	345	Eats raw meat and biscuits; vomited once
125	8	M	13	302	Drinks milk well but slowly
12	9	M	18	394	Eats biscuit well; vomited several times
23	15	F	13	431	Eats meat and biscuits; vomited twice
27	7	F	15	315	Eats well but very slowly

COMMENT

Although the number of experiments performed are few, the constancy of the finding indicates that we are dealing with a definite mechanism capable of producing peptic ulcers of the duodenum. The assumption seems justified that the presence of pancreatic juice in some way protects the duodenum, since its mere diversion to the outside and in the absence of any other demonstrable changes brings about spontaneous peptic ulcers. The present experiments suggest, moreover, that the ulcers produced by experimental "duodenal drainage" and by other similar devices as reported by the many observers previously noted are undoubtedly due, not to the diversion of bile or duodenal secretions or to mechanical factors, but to the absence of pancreatic juice alone. Certainly the location of the lesion at the exit of the stomach and its appearance are similar in all cases, and in the present experiments all other factors have been excluded. Thus the entire gastro-intestinal and biliary tracts were left intact, only the pancreatic ducts being tied and intubated. That the present experiments probably have a greater bearing on the occurrence of this lesion in man is suggested, too, from the fact that

unlike some of the experiments referred to, the lesions develop in duodenal and not jejunal mucosa and in the presence of a normal pylorus and intestinal continuity.

The possibility that bile may also play a part in protecting the duodenum from ulceration is indicated by the experiments already mentioned. It is significant, however, that they were found in a relatively small proportion of the experiments performed and in some were complicated by inanition and other diseases. Bile, moreover, is not an alkaline secretion, as is frequently assumed, but normally is actually acid in reaction.²³ It could not play any part, therefore, in the neutralization of gastric acidity, except possibly by mere dilution. In any case, the rôle of bile must be a minor one as compared with that of pancreatic juice in the development of the duodenal ulcers under discussion.

How may we explain the protective action of the pancreatic juice in these experiments? The assumption may be and has been made that acid gastric contents injure the duodenal mucosa because it is not neutralized by the alkaline pancreatic juice. Extensive study of test meals and fractional analyses of gastric contents has led to the general belief, however, that neutralization of gastric acidity occurs on the proximal rather than the distal side of the pylorus. Recent observations, moreover, have tended to show that this neutralization occurs largely by reflux of pancreatic juice into the stomach. The evidence in support of this theory has been discussed in detail in previous papers from this laboratory.²⁴ The recent observations of Dragstedt and Ellis²⁵ lend further support to this theory. They found that gastric juice collected from the whole isolated stomach always contained a high level (0.4-0.5 per cent) of hydrochloric acid, thus showing the absence of any intrinsic neutralizing mechanism in the stomach itself as claimed by McClean²⁶ and others. Obviously, if this is true, the rôle of the pyloric muscle in controlling reflux is an important one, as will be referred to again.

The defect causing ulceration, according to this theory, lies in the inadequate preparation of gastric contents for reception by the duodenum, more specifically, in its inadequate acid neutralization. This conception is in accord with many of the experiments already referred to. Thus, it shows how the duodenal diversion experiments prevent adequate neutralization of gastric acidity, which remains high, as was directly

23. Drury, D. R.; McMaster, P. D., and Rous, P.: *J. Exper. Med.* **39**:403, 1924.

24. Elman, R.: Probable Influence of Pancreatic Juice in Regulation of Gastric Acidity, *Arch. Surg.* **16**:1256 (June) 1928; *Surg., Gynec. & Obst.* **49**:34, 1929. Olch, I. Y.: Duodenal Regurgitation as Factor in Neutralization of Gastric Acidity, *Arch. Surg.* **16**:125 (Jan.) 1928.

25. Dragstedt, L. R., and Ellis, J. C.: *Am. J. Physiol.* **93**:407, 1930.

26. McClean, H., and Griffiths, W. J.: *J. Physiol.* **66**:356, 1928.

demonstrated by Steinberg and his co-workers.¹⁶ It explains the frequency of jejunal ulcers at a gastro-enterostomy stoma where the pylorus has been occluded or where the duodenal contents have been diverted, since in this way duodenal regurgitation is prevented. The infrequency of marginal ulcers following gastro-enterostomy in cases in which there is actual pyloric stenosis does not necessarily disqualify this explanation, for in these cases the prolonged gastric dilatation and stagnation has already rendered the stomach incapable of developing a normal acidity to begin with.

Further evidence that fits in with this theory is the experimental production of high gastric acidity and ulcers by partial pyloric occlusion. Thus, Friedman and Hamburger²⁷ were able to show an increase in gastric acidity after narrowing of the pylorus by the application of a circular silk suture, an experiment that we performed in this laboratory with similar results. They also showed that following the procedure, experimental defects of the gastric mucosa failed to heal and frequently developed into peptic ulcers. In two dogs, moreover, spontaneous duodenal ulcers were found, one of which had perforated. Bolton²⁸ showed, too, that healing of experimental ulcers was greatly prolonged if a rubber band were placed around the pylorus so as to constrict it. Similar delay has been reported by Ivy.⁵ Hughson,²⁹ in a converse experiment, showed an acceleration in the healing of ulcers if the pylorus were "splinted" so it could not contract. Elman and Rowlette³⁰ finally were able to demonstrate a lowering of gastric acidity as shown by a more rapid neutralization of an acid test meal following successful division of the pyloric muscle.

These observations all tend to explain the correlation between duodenal ulcerations, high gastric acidity and hyperactivity of the pylorus which has long been noted clinically. The development of a high gastric acidity in clinical instances of duodenal ulcerations is explained by the diminished reflux of pancreatic juice due to increased pyloric tone. A number of proved cases of duodenal ulcerations were studied in this clinic and marked diminution of acid neutralization in the stomach noted in all.³¹ Pylorospasm from whatever cause by diminishing duodenal reflux promotes a high gastric acidity which may be the only necessary factor needed to prevent traumatic,

27. Friedman, J. C., and Hamburger, W. W.: *Experimental Chronic Gastric Ulcer*, J. A. M. A. **63**:380 (Aug. 1) 1914.

28. Bolton, C.: *Proc. Roy. Soc., London s.B.*, **82**:233, 1909-1910.

29. Hughson, W.: *Relation of Pylorus to Duration of Experimental Gastric Ulcer*, Arch. Surg. **15**:66 (July) 1927.

30. Elman, R., and Rowlette, A. P.: *The Rôle of the Pyloric Sphincter in the Behavior of Gastric Acidity*, Arch. Surg. **22**:426 (March) 1931.

31. Elman (footnote 24, second reference).

mechanical or other erosions from healing and, indeed, from developing into a peptic ulcer. On the other hand, a pyloric ulcer causes spasm which in turn promotes hyperacidity leading to a vicious circle and progression of the lesion. Pylorospasm itself is known to develop reflexly from other lesions in the abdomen thus explaining the not infrequent association of duodenal ulcerations, appendicitis and cholecystitis. That pylorospasm may occur on a neurogenic basis was promulgated years ago by Eppinger and Hess³² on the basis of their concept of vagotonia. Certainly much clinical study has shown that symptoms of pylorospasm and duodenal ulcerations may develop from or be aggravated by psychic factors presumably mediated through the vagus nerve.

The importance of the pylorus in the treatment for duodenal ulcerations thus lies, in part at least, in its effect on the control of gastric acidity. Various operations have been designed, in fact, aiming, by removal of part of the muscle, to prevent pylorospasm. In a number of cases of pylorospasm without ulcer, Finney and Friedenwald³³ performed a pyloroplasty and achieved clinical cures. Recently Morton³⁴ and Archer³⁵ called attention to cases of hypertrophy of the pylorus in adults on whom the Rammstedt operation was done with complete cures. Further study may show that this simple procedure may be all that is necessary for the relief of early pylorospasm with or without ulcer.

SUMMARY

Spontaneous peptic ulcers were observed in six dogs that lost the total pancreatic juice for thirteen or more days and were kept alive and in good condition by careful feeding and the daily intraperitoneal administration of 500 cc. of Ringer's solution. These observations together with those of others point to the importance of the pancreatic juice in protecting the duodenal mucosa, most likely through its control of gastric acidity by reflux into the stomach. The clinical application of these findings to high gastric acidity, pylorospasm and duodenal ulcer has been briefly discussed.

32. Eppinger H., and Hess, L.: *Vagotomia*, New York, Nervous and Mental Disease Publishing Co., 1915.

33. Finney, M. T., and Friedenwald, J.: *Am. J. M. Sc.* **162**:469, 1921.

34. Morton, C. B.: *Hypertonicity and Hypertrophy of Pylorus in Adults*, *Arch. Surg.* **20**:508 (March) 1930.

35. Archer, V. W.: *Am. J. Roentgenol.* **23**:510, 1930.

THE RELATIVE EFFECT OF CONTRACTION OF THE DIAPHRAGM ON THE BRONCHI OF THE UPPER AND LOWER LOBES*

I. A. BIGGER, M.D.

RICHMOND, VA.

AND

BENTLEY COX, M.D.

LOUISVILLE, KY.

The large number of operations on the phrenic nerve performed in recent years has stimulated interest in the relative effect of contraction of the diaphragm on the upper and lower lobes of the lung. Paralysis of the diaphragm by section of the phrenic nerve was first advised for disease of the lower lobe, but more recently it has been advocated for involvement of the upper lobe also. The question as to which lobe under similar conditions is more benefited by paralysis of the diaphragm is still unsettled. Some surgeons report more favorable results on lesions of the lower lobe; others believe that the upper and lower lobes are equally benefited. With that issue in view, these experiments were carried out.

EXPERIMENTAL METHODS

No method has been devised by which the respired air from an individual pulmonary lobe can be measured satisfactorily, but one would expect the changes in the bronchial length to correspond closely with the changes in the volume of respired air. Therefore, it was decided to determine the changes in the bronchi of the upper and lower lobes produced by contraction of the diaphragm.

The method used to demonstrate the bronchi was that described by Francis.¹ Dogs were anesthetized by barbital intravenously and in the later series by amytal intraperitoneally. A bronchoscope was inserted, and a straight tube with a flexible tip was passed through this for insuf-

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* From the Department of Surgery, Vanderbilt University School of Medicine, Nashville, Tenn.

1. Francis, Byron F.: The Changes in Shape and Size of the Tracheo-Bronchial Tree Following Stimulation of the Vago-Sympathetic Nerve, *Arch. Surg.* **19**:1577 (Dec.) 1929.

flation of the lower lobe and a metal tube with a short 60 degree side-arm was used for insufflations of the upper lobe. Bismuth subcarbonate, thoroughly dried, was insufflated through this tube into the bronchi by compressed air. After the first few experiments it was decided to confine the studies to the bronchi of the right lung, because the upper main bronchus was more accessible and superimposed shadows were avoided on the lateral x-ray plates. The right phrenic nerve was exposed and divided, and the distal end was stimulated by a faradic current. Two

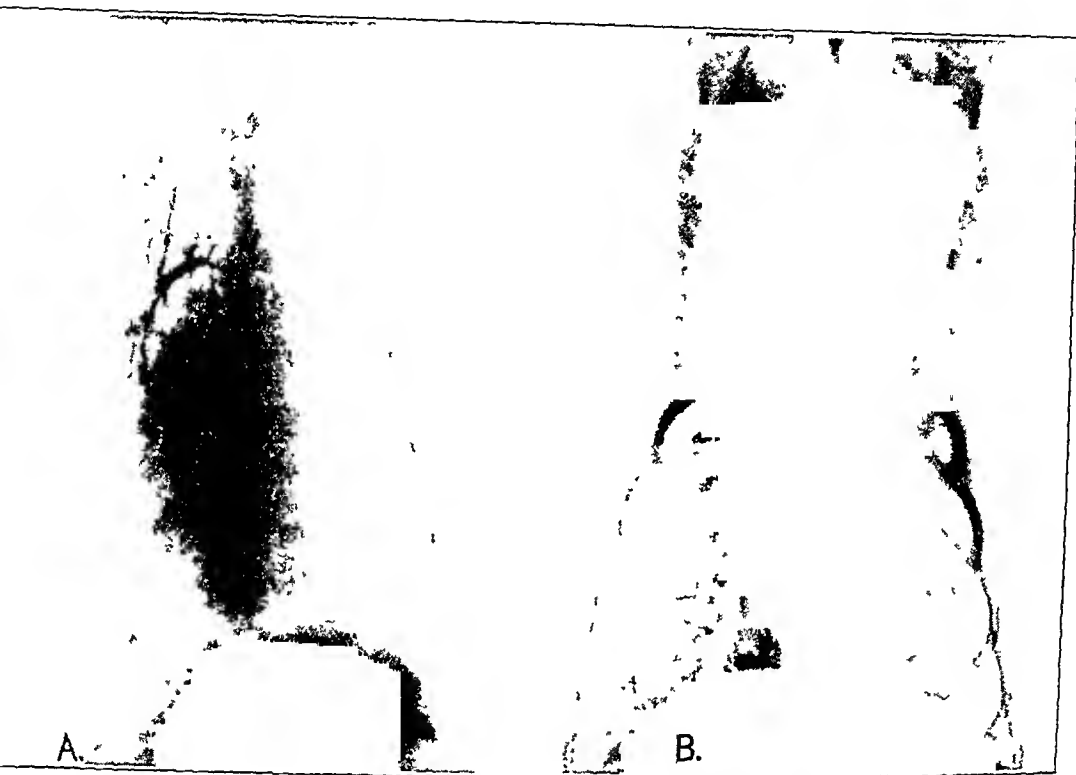


Fig. 1 (dog 17).—Roentgenograms made in the dorsal position *A* shows marked contraction of the right side of the diaphragm with lengthening of the bronchi; *B*, shortening of the bronchi during expiration.

roentgenograms were made with the dog in the dorsal position, one while the nerve was being stimulated and another at expiration with the nerve divided. Then the dog was turned on the right side (care being taken to have the sternum on the same level with the spine), and two more roentgenograms were made, one while the nerve was being stimulated and another at expiration. All were made at a distance of approximately 6 feet. Points anatomically identical in both the bronchi of the upper and lower lobes were selected in those made in the dorsal position, and the distance between these points measured. The angle of deviation of the

bronchi from the perpendicular was determined in the two lateral plates and used to calculate the length of the bronchi. The following formula was used to compute the actual length:

$$\text{Actual length} = \frac{\text{Length measured on dorsal plate}}{\text{Cosine of angle of deviation in lateral plate}}$$

Twenty-eight experiments were carried out, but only eight were considered satisfactory for measurements. The first experiments were

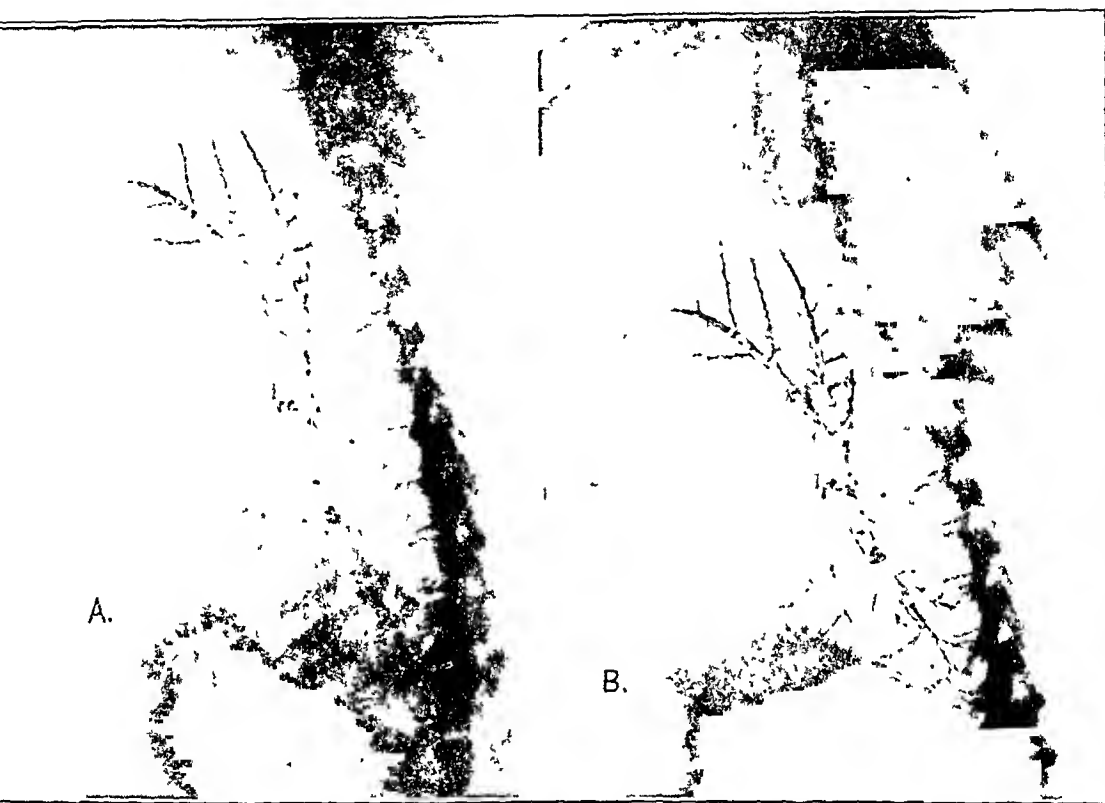


Fig. 2 (dog 17).—Roentgenograms made in the lateral position. *A*, made during contraction of the right side of the diaphragm, shows how the bronchi approach the horizontal when the dog is in the dorsal position. *B*, made during expiration, shows how they deviate from the horizontal when the dog is in the dorsal position.

unsatisfactory because too much bismuth had been insufflated, with the result that the bronchi were occluded, which prevented an expansion of the lung and lengthening of the bronchi. In the later experiments, only a very small amount of bismuth was insufflated, with much better results. Typical plates are shown in figures 1 and 2. Table 1 gives the length of the bronchial shadows and angles of deviation from the perpendicular, and table 2, the calculated length of the bronchi.

TABLE 1.—*Measurement of the Length of the Bronchi in the Dorsal Plates and of the Angle of Deviation in the Lateral Plates*

Dog	Lobe of Lung	Length of Bronchi in the Dorsal Plates, Mm.		Deviation from the Perpendicular in the Lateral Plates, Degrees	
		During Stimulation of Phrenic Nerve	At Expiration	During Stimulation of Phrenic Nerve	At Expiration
		(1)	(2)	(3)	(4)
16	Right upper.....	40	29	52	52
	Right lower.....	86	57	14	26
17	Right upper.....	55	46	0	0
	Right lower.....	89	66	10	10
18	Right upper.....	41	31	57	59
	Right lower.....	68	47	27	33
19	Right upper.....	55	40	10	15
	Right lower.....	115	71	15	29
20	Right upper.....	42	32	50	53
	Right lower.....	87	54	13	32
21	Right upper.....	31	24	37	47
	Right lower.....	56	46	10	17
24	Right upper.....	44	31	35	45
	Right lower.....	82	55	15	25
28	Right upper.....	36	32	24	26
	Right lower.....	58	51	21	24

TABLE 2.—*Percentage Lengthening of the Bronchi During Stimulation of the Phrenic Nerve*

Dog	Right Upper Lobe	Right Lower Lobe
16.....	38	39
17.....	19	34
18.....	25	33
19.....	34	46
20.....	30	41
21.....	8	16
24.....	23	40
28.....	12	13
Average.....	21	34
Difference.....		13

REVIEW OF LITERATURE

No experiments bearing directly on this subject could be found in the literature. Walsh,² in a clinical and pathologic study, concluded that the activity of the lung was greatest at the apex and least at the base. Sergeant³ was able to demonstrate by x-ray studies that the greatest activity occurred in the anterolateral portion of the lung and the least activity posteriorly and at the apex.

2. Walsh, Joseph: Pulmonary Activity Greatest at the Apex and Least at the Base, *Am. Rev. Tuberc.* **14**:142, 1926.

3. Sergeant, E.: The Motor Independence of Pulmonary Lobes, *Semaine d. hôp. de Paris* **3**:157, 1927.

COMMENT

Walsh concluded that the pulmonary activity was greatest at the apex and least at the base on the basis: first, that pulmonary tuberculosis develops most frequently in the upper portion of the lung, and even miliary tuberculosis advances more rapidly in the upper lobe; second, that the pulmonary alveoli are larger at the apex than at the base in the normal lung. In emphysematous lungs, the alveoli are greatly dilated at the apex and only slightly dilated at the base.

No logical explanation has yet been offered for the fact that pulmonary tuberculosis develops usually in the upper portion of the lung, but the fact remains that the earliest lesions are not in the extreme apex but in the infraclavicular region. If the question were entirely one of greater activity as stressed by Walsh, one would expect the earliest lesions in the extreme apex. He laid greatest stress on the enlargement of the apical alveoli. This is an anatomic fact, but it would appear that respiration plays a relatively small part in the dilatation of the alveoli, as the intrapulmonary pressure does not reach atmospheric pressure during any phase of normal breathing. Coughing and straining raise the intrapulmonary pressure above atmospheric pressure, so they would be expected to play a large part in the dilatation of the alveoli. During increased intrapulmonary pressure, the lung distends at the point of least outside support, which is at the apex.

The ideas presented in this paper agree much more closely with those of Sergent. While he does not attempt to discuss the question of the part played by the thoracic wall and diaphragm in the activity of the lung, he does believe that the activity of the lung, as the result of movement of the thoracic wall, is less at the apex posteriorly and greater below and in front. It seems logical to suppose that the effect of contraction of the diaphragm acting through an elastic pulmonary tissue would be greatest at the base, and would diminish as the distance from the diaphragm increased.

In this series of experiments the percentage lengthening of the bronchi of the lower lobe was uniformly greater than that of the upper lobe, and the percentage difference varied directly with the degree of contraction of the diaphragm. If the change in bronchial length is taken as an indication of the change in respired air, contraction of the diaphragm produces a slightly greater effect on the lower than on the upper lobe. However, this difference is so slight during normal respiration that it is of no practical importance.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

E. STARR JUDD, M.D.
ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.
ROANOKE, VA.

JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES
AND

ALEXANDER B. HEPLER, M.D.
SEATTLE, WASH.

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URETHRA

Tumor.—Schiftan³⁹ reported 5 cases of papillomatosis of the urethra observed in the last two years in the dermatologic clinic of the Britz Hospital in Berlin. There was one case of multiple papillomatosis of the anterior urethra. In all of the cases there was a history of previous gonorrheal infection.

The papillomas were treated by electric cautery. A proprietary cocaine mixture was used as a local anesthetic. In spite of the care in protecting the urethra at the time of treatment, a beginning stricture was noticed while the patient was still under treatment. The prognosis in these cases is poor because of the possibility of malignant changes.

[ED. NOTE.—Polyps and papillomas of the urethra are not uncommon. They are usually very small and the result of long and tedious urethral infections. They have little clinical significance. In most cases they disappear following treatment for the underlying infection. Both the small and the large tumors respond readily to fulguration or snaring. Those occurring in the posterior urethra of male patients may be pedunculated and occasionally interfere with the closure of the internal sphincter; those occurring near the external orifice are generally flat and sessile. Multiple and extensive growths are occasionally seen. Zuckerkindl reported a case in which a papillomatous growth covered the entire urethra. There is a tendency to rapid and extensive recurrence after removal. Elder and Lewin both reported cases in which the recurring papilloma completely filled the urethra.]

39. Schiftan, Walter: Papillomatosis der männlichen Harnröhre, Ztschr. f. Urol. **24**:518, 1930.

Valve Obstruction.—Campbell⁴⁰ reported 18 cases of congenital obstruction of the posterior urethral valve, all occurring among children. Urethral valves are the most common congenital infravesical obstruction, and because they are confined to the prostatic canal are limited to male patients. When because of situation or size the valves produce symptoms, the clinical manifestations are those of obstruction; secondary symptoms are those of uremia. Diagnosis is made by cysto-urethroscopy, and the prognosis is directly proportional to the renal function.

Structurally, valves may be present only as low ridges; these do not obstruct. More often valves appear as mucosal folds or redundances and, in retarding a fluid stream, may be cystoscopically observed to balloon into cusp formation. They may also be present as partial or complete diaphragms. Most valves are contiguous with the verumontanum at some point and usually pass from the anterior end of the verumontanum to the lateral urethral walls; in several instances extension from the posterior verumontanum to the outlet of the bladder was observed. Segments of valves of the latter type are likely to be multiple; six or seven folds may extend from the verumontanum posteriorly into the outlet of the bladder. Valves may be unilateral. The valve may be totally independent of the verumontanum, situated either anterior or posterior to this organ. In the presence of valves, the verumontanum is usually anomalous; enlargement and great elongation is the rule. Sometimes the verumontanum extends from the vesical outlet anteriorly for 2 or 3 cm.

The pathologic changes in the urinary tract are those common to all infravesical obstructions. Until prolonged back pressure causes muscular decompensation, the wall of the bladder shows trabeculation, hypertrophy and sometimes inflammation, and may be the site of the diverticulum. Often there is trigonal hypertrophy. With decompensation, the bladder becomes a large, hypotonic bag. Ureteral and pelvic dilatation occur as the disease advances; urinary back pressure, as well as inflammatory changes, destroys the ureterovesical valve, so that vesico-ureteral reflux is demonstrable in most advanced cases. The ureters may become larger than the colon; the renal parenchyma is frequently compressed to a thin shell. Nephritis from compression, with infection, leads to reduction of renal function as the disease progresses.

Urinary frequency is the most common symptom and is usually present from birth. After infection has set in, the child may urinate every twenty to thirty minutes. In many instances overflow incontinence may keep the child continually wet, and the condition will be diagnosed

40. Campbell, M. F.: Obstruction of the Posterior Urethral Valve in Infancy and Childhood, J. A. M. A. 96:592 (Feb. 21) 1931.

as enuresis. Dysuria is due to the diminished urethral caliber and is often distressing. Chronic distention of the bladder is sometimes manifest by protuberance of the lower part of the abdomen; frequently the mother or the patient has palpated the vesical mass.

Laboratory examination discloses urinary infection in most instances. In advanced cases, the urinalysis often leads to the diagnosis of chronic interstitial nephritis.

Treatment should be removal of the obstruction, but this should not be attempted until the condition of the patient warrants surgical procedures. If the residual urine is more than 3 ounces (90 cc.), gradual decompression and continuous drainage of the bladder should be carried out until functional stability has been established. If the residual urine is less than 90 cc., preliminary drainage for a few days is excellent practice. Several methods of removal of the valve have been advocated. Perineal approach is unsatisfactory and unnecessary. If the urethra is impassable or drainage has been instituted by cystotomy, suprapubic attack may be carried out. Fluid in abundance is the best medicine after operation. If the obstruction has been properly removed, urination will be free.

Trichomonas Infection.—Riba⁴¹ reported several cases of trichomonas urethritis and observed that the presence of the trichomonas is not limited to the female genital tract, but may occur in the male. Urethritis of the male patient may be complicated with prostatovesiculitis. The motile protozoa may be readily demonstrated in fresh wet preparations, and the nonspecific urethral and prostatic secretions should be examined in their natural state.

PENIS

Carcinoma.—Colby and Smith⁴² reported a study of 50 cases of carcinoma of the penis to determine the correlation of the degree of malignancy of tumors, as determined by their histologic appearance, and their clinical course. With the histologic appearance as a basis, the tumors were graded as to malignancy into low and high. Twenty-six cases were of low grade and 24 of high grade. Partial amputation was performed in 27 cases, total amputation or emasculation in 16, minor operative procedures or radium in 7, and one or both groins were dissected in 32.

The average age of the patients was 59 years. Definite phimosis had existed in about half the cases, and, as far as could be determined, none of the patients had been circumcised in infancy or early childhood.

41. Riba, L. W.: *Trichomonas Urethritis*, J. A. M. A. **96**:2100 (June 20) 1931.

42. Colby, F. H., and Smith, G. G.: *Carcinoma of the Penis*, J. Urol. **25**:461 (May) 1931.

Thirty-eight (76 per cent) of the 50 patients were traced after operation at varying intervals up to ten years. In comparing the post-operative course of the two groups, it was found that 10.5 per cent of those with tumors of low grade malignancy died of carcinoma within the first two years, and 36.8 per cent of those in which the malignancy was high died of carcinoma within the first year. In the first group a higher proportion of patients were living for a period of years than in the second group.

The advisability of dissection of the groin seemed to be important. Of the entire 14 cases of both groups in which the groins were not dissected, 75 per cent of patients in the first group and 83.3 per cent in the second group lived for varying intervals without evidence of carcinoma. None of the patients of the first group died of the malignant lesion, while one patient (16.6 per cent) of the second group died. In 10 of the 14 cases partial amputation was performed, in 3 circumcision alone, and in 1 case radium alone was applied.

In the 24 cases in which the groin was dissected, 63.6 per cent of patients of the first group and 38.4 per cent of the second group are living for varying intervals free from carcinoma. Eighteen per cent of patients of the first group and 46.1 per cent of the second group died of the disease. In the series of 50 cases the groin was dissected in 32 (64 per cent). In 24 per cent of cases in the first group and in 62 per cent of the second group, malignant nodes were found on microscopic examination, showing a greater tendency for the more malignant type of tumor to involve the lymph nodes. Of the cases in which malignant nodes were found, 50 per cent of patients of the first group and 70 per cent of the second group died of carcinoma. In 11 of the 50 cases, the groin was dissected although nodes had not been palpable. In 4 (36.3 per cent) of these cases, malignant nodes were found on microscopic examination.

It is Colby and Smith's belief that dissection of the groin should be performed as a routine part of the operative treatment for carcinoma of the penis except in cases in which the disease has existed only for a short time. Conservative surgical measures, such as excision or irradiation, may often be employed, with a reasonable expectation of cure.

Barney,⁴³ in a follow-up study of 90 cases of carcinoma of the penis, found that phimosis of long duration had occurred in 85 per cent. As a corollary they found that if circumcision had not been performed in infancy or childhood, carcinoma did not develop. Most deaths from carcinoma of the penis are due to internal metastasis which may occur without involvement of the inguinal nodes, or even if they are excised. The deep lymphatic glands of the penis are as efficient in

43. Barney, J. D.: Discussion, *J. Urol.* 25:482 (May) 1931.

carrying metastatic cells as are the more superficial ones which pass to the groin. In giving a prognosis in such cases, this fact should be taken into consideration.

TESTIS AND EPIDIDYMIS

Tumor.—Von Illyés⁴⁴ reported a case of hypernephroma of the testis. Many years ago an operation had been performed on the left undescended testis. The testis had been enlarged for two years, and when examined it measured about 10 cm. in diameter and was irregular. The epididymis was also enlarged because of the presence of hydrocele. Cystoscopic examination revealed that the urine from the left kidney was thick and purulent. The right side was normal. The left kidney was removed, and the ureter was found to be compressed by tumor. Later, the enlarged testis was removed. Microscopic examination of both specimens revealed hypernephroma. Although the metastatic growth in this case was small, owing to its position it compressed the ureter and caused infected hydronephrosis.

Undescended Testis.—Goetsch⁴⁵ reviewed 32 cases of undescended testis and summarized his observations as follows: There is no evidence that an undescended testis properly placed in the scrotum has any greater malignant potentialities than the testis that has always been in normal position. Undescended testis is practically always accompanied by congenital hernia. Sacrifice of the undescended testis is not warranted, since most of them, including those in the abdomen, can be satisfactorily placed in the scrotum by the Bevan operation. Undescended testes lose the power of spermatogenesis but continue to elaborate internal secretion. The scrotal position is necessary for complete anatomic and physiologic development of the testis. Even the atrophic testis with questionable spermatogenesis should be conserved for the influence it may exert in the development of the secondary sex characteristics. Spermatic circulation should not be eliminated if mobilization is at all possible without division. Loss of the spermatic circulation invariably leads to marked atrophy and sometimes to complete atrophy.

UROGRAPHY

Braasch⁴⁶ reviewed a series of 40 cases of proved renal lithiasis, in which intravenous urography was done. This procedure was of particular value in identification of shadows, determination of the intra-

44. von Illyés, Géza: Hypernephrom des Hodens, mit einem zweiten Ureter-Kompression verursachenden Herd, *Ztschr. f. urol. Chir.* **30**:70, 1930; abstr. in *Am. J. Cancer* **15**:506 (Jan.) 1931.

45. Goetsch, Arthur: Undescended Testis: Review of Thirty-Two Operative Cases, *Am. J. Surg.* **12**:63 (April) 1931.

46. Braasch, W. F.: The Value of Uroselectan in Renal Lithiasis, *J. Urol.* **25**: 265 (March) 1931.

renal situation of shadows, ascertaining the differential renal function, demonstration of coincident disease or anomaly in the affected kidney and determination of the functional capacity and disease or abnormality in the other kidney.

The only advantage of intravenous urography over the retrograde method in the identification of renal shadows is that it can be used as a routine in many cases in which cystoscopic examination might not be advisable. Shadows that are seemingly intrarenal or extrarenal on interpretation of the original film often prove to be the opposite in the intravenous urogram. In doubtful cases, both methods of pyelography should be employed. Small shadows in the renal pelvis, which do not cause stasis, occasionally may remain unidentified by intravenous urography because of lack of detail in the minor calices. By intravenous urography, exposures can be made with the patient in different positions, and the kidney may be displaced so as to determine differences in the relative position of the pelvis and of the shadow in question. In this type of procedure the density of the pelvic shadow is usually less than that of the calculus, and as a result the outline of the calculus commonly can be seen through that of the pelvis. In some cases the density is not then visible. It has particular value in cases of stones situated in the ends of the calices, since it gives a better idea than retrograde urography as to their exact position and the feasibility of their removal.

The visual estimate of renal function made possible by intravenous urography is often more accurate and satisfactory than the usual tests of renal function in the presence of renal calculus. Both the test with phenolsulphonphthalein and that with indigo carmine are misleading in determining the functional capacity of a kidney which contains a calculus. Iopax gives evidence which leads to the belief that bilateral involvement of the kidney occurs more commonly than previously was supposed.

Retrograde urography, with stone in the ureter, frequently is followed by serious febrile reactions, particularly when there is pyelectasis and when renal drainage is obstructed. Intravenous urography obviates this and often furnishes diagnostic data not possible with retrograde urography.

Bugbee and Murphy⁴⁷ stated that, in any new discovery, the tendency has been to overestimate the possibilities of its usefulness. They believe that intravenous urography is primarily a method of corroboration, to be employed as a supplement to the present methods of urologic diagnosis, except in the limited number of cases in which cystoscopic manipulation is impossible. In such cases it gives valuable

47. Bugbee, H. G., and Murphy, A. J.: The Value and Limitations of Uroselectan as an Aid in Urological Diagnosis, *J. Urol.* **25**:275 (March) 1931.

data otherwise unavailable, but when unsupported by cystoscopic information the interpretations must be made with extreme care and conservatism.

Lowsley⁴⁸ stated that in a series of 45 cases intravenous pyelography with iopax was found a helpful adjunct, particularly in tuberculosis of the urinary tract. When the serious general condition of certain patients with tuberculosis precludes cystoscopic examination, intravenous pyelography frequently furnishes sufficient information so that further investigation is unnecessary.

Herbst⁴⁹ stated that iopax may be used in practically all cases in which the cystoscopic pyelogram is used, and also in some cases in which the retrograde method is inadvisable or impossible. Tumor of the kidney, polycystic kidney and early renal tuberculosis cannot be studied as satisfactorily by the use of iopax as by cystoscopic examination. Interpretation of intravenous films is difficult if there is gas in the bowel and the torso is thick. Iopax will be particularly valuable in the diagnosis of urologic disorders of children. It will often be used in preference to cystoscopic examination, thus avoiding a general anesthetic and its attendant difficulties.

Von Lichtenberg⁵⁰ formulated the indications and limitations of intravenous urography by clinically interpreting the results in more than 700 cases. One hundred cubic centimeters of a 40 per cent solution of iopax was used, the first picture taken a quarter of an hour, the second three-quarters of an hour and the third an hour and a quarter after intravenous injections.

By intravenous urography with iopax, visualization of the urinary tract and the relationship between various parts of the urinary tract may be obtained. Important data concerning renal function may also be obtained by roentgenologic means and by qualitative and quantitative chemical data. It also enables interpretation of the dynamics of the urinary tract by observing the expulsion of iopax. A good picture is expected only when renal function is satisfactory, because the intensity of the roentgen ray is dependent mostly on the function of the kidney.

Intravenous urography can be used in cases in which cystoscopic examination fails or is unusually difficult, if catheterization of the ureters or instrumental pyelography cannot be done, or if this method does not afford definite information. It can also be used in cases in which instrumental pyelography should not be done, because of the

48. Lowsley, O. S.: Uroselectan in Urinary Tuberculosis, *J. Urol.* **25**:293 (March) 1931.

49. Herbst, R. H.: Comparative Value of Uroselectan to Cystoscopic Pyelography, *J. Urol.* **25**:287 (March) 1931.

50. von Lichtenberg, Alexander: The Principles of Intravenous Urography, *J. Urol.* **25**:249 (March) 1931.

possible injury that might result. It affords full information concerning the urinary tract in cases of urethral strictures, severe disease of the bladder, bleeding, ruptured kidneys, fistulas, in cases of transplanted ureters and in the examination of young children.

Beer⁵¹ stated that fluoroscopy of the exposed kidney in the search for stones was advanced by Braasch and proved of great aid in localizing fragments of stone that might be removed at the time of operation. Experience demonstrated that small fragments escaped the attention of the fluoroscopist, and frequently were recovered by palpation and irrigation, after the kidney was thought to be empty, or were seen in a few weeks in control pictures during convalescence. Quinby then suggested that a small film be placed against the exposed wall and well delivered kidney and a roentgenogram made.

Beer expressed the belief that every fragment of stone not recovered by roentgenographic control on the table, or by irrigation or drainage through a nephrostomy tube, is a potential source of danger to the patient and often counteracts attempts at a complete and definite cure. For the last five years he had been using roentgenograms as controls in operations for stone in the kidney. The method of making films of the kidney by means of the improved cassette and intensifying screen is used regularly in all complicated cases and in all cases of multiple calculi. Roentgenographic control has repeatedly shown stones or fragments in the cavities of the kidney or parenchyma, even after careful search and prolonged, forceful irrigation of the pelvis and calices. In cases in which fragments are left behind, it is Beer's custom to drain by nephrostomy and to irrigate in the hope that unrecovered fragments may be discharged spontaneously or be washed out.

In more than 50 complicated cases of stone, roentgenographic control of the exposed kidney was used. Small fragments and even sizable stones were overlooked in a relatively large percentage of cases, after complete removal had ostensibly been carried out and after thorough irrigation of the pelvis of the kidney and calices. In the majority of these checked cases the fragments or stones were removed after localization by the roentgenogram.

[ED. NOTE.—The prevention of recurrence of urolithiasis demands thorough operative removal of all stones or fragments of stones, the elimination of infection and the establishment of adequate drainage of the urinary tract. The first consideration is of paramount importance, as many so-called recurrences have been the signs of incomplete operative removal of calculi.

51. Beer, Edwin: Roentgenological Control of Exposed Kidneys in Operations for Nephrolithiasis, with the use of Special Intensifying Cassette, *J. Urol.* 25:159 (Feb.) 1931.

The use of the fluoroscope at the operating table, as developed by Braasch and Carman, was of the utmost value in localizing stones or fragments which otherwise would have been overlooked. The cassettes described by Beer and Benjamin perhaps give a better opportunity to pick up fragments of stone, and thus represent a further advance in the use of the roentgen ray in the surgical removal of renal calculus.]

Benjamin⁵² stated that in about 25 to 50 per cent of the cases of renal lithiasis checked by the control roentgenograms, stones had been incompletely removed, although the operations were performed by competent urologic surgeons. Stones 1.5 cm. in diameter had been overlooked. Interpretation of control roentgenograms of the kidney is not without its inherent difficulties. The presence of blood clots, coagulated tissue fluids and overlapping detached soft tissues, may be confusing. It is essential to read the film while it is wet.

A special small cassette measuring $3\frac{3}{4}$ by $4\frac{3}{4}$ inches (8 by 10 cm.) has recently been designed by Jaches; this has an aluminum cover and contains a double intensifying screen. It reduces the exposure time to a tenth of that of the ordinary film and insures sharp, clear pictures, even with the patient under light anesthesia. The cassette is firm and not subject to buckling, thus eliminating artefacts which occurred with the use of the ordinary film. It is readily kept clean and easily and rapidly reloaded. Exposure is made from in front of the patient. The time is about half a second or less, at a distance of about 30 to 48 cm. Guide needles are inserted into the exposed kidney by the surgeon. The loaded cassette is dropped into a sterile rubber bag the inside of which has been carefully wiped dry, and the cassette is then tucked behind the kidney, care being taken to cover it entirely; if this cannot be done, the portion of the kidney under suspicion is covered. Either side of the cassette may be used against the kidney.

NERVE CONTROL OF KIDNEY, URETER AND BLADDER

Harris and Harris⁵³ stated that in a large number of cases in which there is renal pain without demonstrable abnormalities except positive response to a test for pain, delayed emptying time of the pelvis and perhaps slight clubbing of the calices which increases renal sympatheticotonus are the cause of the symptoms and that renal denervation will give relief.

Since the introduction of pyeloscopy these authors have been able to demonstrate motor disturbances of the renal calices, pelvis and ureters

52. Benjamin, E. W.: Notes on the Technique of X-Ray Control in the Operating Room, *J. Urol.* **25**:165 (Feb.) 1931.

53. Harris, S. H., and Harris, R. G. S.: Renal Sympathetico-Tonus, Renal Pain and Renal Sympathectomy, *Brit. J. Urol.* **2**:367 (Dec.) 1930.

and have defined the urographic evidence of renal sympatheticotonus and the indications for sympathectomy as: (1) irregular and incomplete contractions of the calices and the renal pelvis; the condition is a fibrillation with interference with the normal peristaltic rhythm; (2) marked slowing with irregularity and increased power of the contractions, associated generally with dilatation of the renal pelvis and clubbing of the calices; delayed emptying time is a feature also, and (3) dilatation and immobility of a single calix with delayed emptying time, and localized sympatheticotonus.

With these urographic observations, a positive pain reproduction test, evidence of generalized sympatheticotonus, with negative urinary findings, and the proved absence of any organic lesion, renal denervation may be undertaken with the assurance that there will be complete and permanent relief from pain. The operation consists in denudation of the vessels of the renal pedicle, working from within outward toward the kidney. The pelvis and first inch of the ureters are also freed of connective tissue.

Farrell⁵⁴ studied the vesicorenal reflexes and the possibility of a renorenal reflex. Twenty-five dogs were used in the experiments, which were performed under morphine and ether anesthesia because it was fairly uniform and exerted little influence on the flow of urine.

It was observed that both distention of the bladder and stimulation of the pelvic nerve produced a change in the renal volume and inhibition of the urinary flow which might be partial or complete. No change in urinary flow resulted from stimulation of the hypogastric nerve, nor, when the splanchnic nerve was sectioned, from the distention of the bladder or stimulation of the pelvic nerve. Distention of the renal pelvis on one side caused inhibition of flow of urine and vasoconstriction of the vessels of the opposite kidney which was manifested by reduction in volume of the kidney. This reduction in volume can be magnified if a diuretic such as dextrose is injected immediately before the distention of the renal pelvis. During urination, urine did not flow from the ureters, apparently a protective mechanism to prevent back pressure on the kidney.

Farrell concluded that many of the impulses arising from the afferent nerves to the bladder traverse the pelvic nerve. Most of the efferent fibers in the splanchnic nerve to the kidney are probably vasomotor. A reflex relation exists between the bladder and kidneys. When the bladder is distended, the flow of urine is diminished, probably a protective mechanism to prevent pressure within the renal pelvis. In clinical cases of retention of urine, when the bladder is chronically distended, this reflex apparently is destroyed, since in many such cases

54. Farrell, J. I.: A Study of Vesicorenal Reflexes and of the Possibility of a Renorenal Reflex, *J. Urol.* 25:487 (May) 1931.

hydro-ureter and hydronephrosis develop. Clinically, reflex inhibition of secretion of urine has been observed following operations on the kidney and others organs, and experimentally, distention of one renal pelvis produces pain, decrease in the blood pressure and inhibition of the flow of urine on the opposite side. Although it is probable that this inhibition is the result of vasomotor changes within the kidney, it is possible to influence the urinary secretion of one kidney by distending the pelvis of the opposite kidney. If this interpretation is correct, it would serve to substantiate the existence of a renorenal reflex.

Wharton and Hughson⁵⁵ reported two cases of persistent and severe ureteral pain. The patients were definitely relieved at first by ureteral dilatation. When this failed to give relief from pain, ureteral denervation accomplished complete cure in both cases. One patient has been well for almost six years, the other for three and a half years.

The interpretation of the condition of the ureter was difficult. In no instance was there any obstruction to the passage of a number 8 renal catheter. In all cases wax bulbs approximately 4 mm. in size hung on being withdrawn. In only one of the three ureters was there dilatation of hydronephrosis. The urine was sterile and clear. The condition did not indicate any intrinsic diminution of the caliber of the ureter and excluded organic ureteral obstruction and stricture, but seemed to signify a persistent state of spasticity. The fact that denervation of the ureter cured the condition entirely apparently substantiates this. Denervation in these cases was not followed by evidence of ureteral or renal dysfunction. The marked decrease in the sensitiveness of the ureter after denervation was shown by postoperative urologic study.

[ED. NOTE.—Again we meet the problem of pain referred to the urinary tract with little if any pathologic change demonstrable grossly. In this country urologists, after Hunner, have attempted to ascribe the underlying causes for the most part to ureteral stricture, ureteral kinks and similar conditions. Ureteral dilatation as a means of relief, although never uniformly accepted or popular, has held and still holds a prominent place in treatment.

During the last five years a newer concept of neuromotor dysfunction as a cause of painful hydronephrosis, of persistent renal and ureteral spasms and of so-called nephritis dolorosa, has become prominent. Denervation procedures such as those of Legueu and Papin have been reported with variable results. The reports of Harris and Harris, and Wharton and Hughson reflect the influence of this application of neuroexeresis to urologic conditions.

55. Wharton, L. R., and Hughson, Walter: Denervation of the Ureter, *J. Urol.* 25:145 (Feb.) 1931.

Much controversial opinion exists, especially among the more conservative observers, with regard to the significance of minor changes from the normal in interpreting urograms. Thus the slight clubbing of single calices, hyperperistalsis of the ureter and pelvis, slight pyeloc-tasis and ureteral dilatations are frequently considered within the range of normal, especially in the absence of stone or infection.

The fact remains that frequently persistent disabling pain referable to the kidney and ureter is observed, and ureteral dilatation often gives relief for a time at least. However, some conditions are resistant, and in these the principles of neurosurgical denervation may be applied with some prospect of relief as Wharton and Hughson have outlined.]

Papin ⁵⁶ stated that all denervation of the ureter follows the blood supply. Following each vessel there is a plexus of nerves that comes to a different level in the ureter. As soon as they arrive at the ureter, the normal plexus communicates above and below. Both the arteries and the nerves anastomose and form this plexus. In order to denervate the ureter, it would be necessary to remove the nerve from each of the small arteries.

Nerve Control.—Gurdjian ⁵⁷ stated that retention is the first manifestation of urinary dysfunction in traumatic myelitis. Severe injury to the cord is not always associated with urinary dysfunction. The evolution of urinary disturbances in traumatic myelitis is usually: (1) retention, or retention with overflow; (2) a period of retention with active incontinence or retention alternating with voluntary urination; (3) active incontinence or complete recovery of function, and (4) in cases with active incontinence with urinary infection, complete incontinence or constant dribbling may develop. The period of retention varied on the average from three to five weeks. Extreme distention of the bladder favors return of function or the production of automatic bladder. In a case of infected bladder with distention, the patient should be placed on continuous drainage or catheterized at frequent and regular intervals. Urinary antiseptics and mild irrigation of the bladder are also indicated.

Learmonth ⁵⁸ considered the principal sources of nerves to the bladder and posterior urethra. These are mainly the presacral nerve, the pelvic nerve and the pudic nerve. The presacral nerve contains fibers that are: (1) inhibitory to the expulsive muscles of the bladder; (2) motor to the muscle around the ureterovesical orifices; (3) motor to the muscle of the trigone; (4) motor to the internal sphincter;

56. Papin, E.: Discussion, J. Urol. **25**:181 (Feb.) 1931.

57. Gurdjian, E. S.: Urinary Tract Manifestations in Traumatic Myelitis, Am. J. Surg. **12**:112 (April) 1931.

58. Learmonth, J. R.: The Nerves of the Urinary Bladder in the Human Being, Proc. Staff Meet., Mayo Clinic **6**:182 (March 25) 1931. ₀

(5) motor to the smooth muscle of the prostate gland; (6) motor to the smooth muscle of the seminal vesicles and ejaculatory ducts; (7) afferent, conveying impressions of distention of the bladder; (8) afferent, conveying impressions of pain on spasmodic contraction of the bladder, and (9) vasoconstrictor to the vessels of the bladder. The pelvic nerves contain fibers that are: (1) motor to the expulsive muscles of the bladder; (2) inhibitory to the internal sphincter; (3) afferent, for the micturition reflex, and (4) afferent, for tactile and painful impulses from the bladder, and, at least in part, from the posterior urethra. The pudic nerve is said to supply some sensory fibers to the posterior urethra; it provides motor nerves for the external sphincter. Apparently integrity of the pelvic nerves alone is essential for the act of micturition.

[ED. NOTE.—Section of the nerve, stimulated by the work of Hunter and Royle, has been done for a variety of neurospastic conditions during the last decade. Learmonth's anatomic study following up the work of Laux and Latarget with regard to the innervation of the bladder is timely and promising. By sectioning the presacral nerve in certain types of paralysis of the bladder, the function of micturition of the pelvic nerves (these being intact) has been reestablished in a few instances. Although this work is still in the developmental stage, the initial results are encouraging and seem to make the procedure worthy of further clinical trial in the hands of the trained, conservative neurosurgeon.]

SURGERY OF THE GENITO-URINARY SYSTEM

Walters⁵⁹ reported that in 1930 at the Mayo Clinic, 1,247 operations were performed on the urinary tract. Three hundred eleven operations were performed on the kidney, with 10 deaths (3.2 per cent). Nephrectomy was done in 165 cases, 7 deaths occurring (4.2 per cent).

There were 10 cases of hydronephrosis in which plastic operations were performed on the renal pelvis. Eight of these operations consisted of resection of the renal pelvis or plastic operation on the obstructed ureteropelvic juncture.

Of 137 operations for nephrolithiasis, pelviolithotomy or nephrolithotomy with preservation of the kidney was performed in 95 cases, and nephrectomy was necessary in only 42. These 42 cases were mainly instances in which the renal parenchyma was largely destroyed or badly infected. Two deaths occurred following operations for nephrolithiasis, both the result of pyelonephritis. Seventy-seven patients were treated for ureterolithiasis. Ureterolithotomy was performed on 50 of the 77 patients, with 2 deaths, 1 of which was due to pulmonary

59. Walters, Waltman: Report of Urologic Surgery (Exclusive of Gynecologic Surgery) for 1930, Proc. Staff Meet., Mayo Clinic 6:98 (Feb. 18) 1931.

embolism. In the remaining 27 cases the stone was removed by manipulation through the cystoscope by means of ureteral catheters.

Eight patients were operated on for exstrophy of the bladder or for complete epispadias and absence of the urinary sphincters, without deaths. In 7 of these cases both ureters were transplanted into the rectosigmoid, and the bladder was removed. It is noted that in 74 cases of exstrophy of the bladder, the ureters have been transplanted to the rectosigmoid, and the exstrophied bladder has been removed at the Mayo Clinic in the last seventeen years. In this series, 3 patients died from operation (4.2 per cent). In a recent study of these cases, it was found that approximately 81 per cent of patients have had good results from operation, and 14 per cent have had fair results.

In a case of extensive malignant lesion of the bladder in which segmental resection could not be performed, the ureters were transplanted into the sigmoid, and total cystectomy was successfully performed. The prostate gland was removed at the same time with total cystectomy. In one other case of contracted bladder, the result of healed lesions of tuberculous, and in which one kidney had been removed, the patient recovered following transplantation of the ureter of the remaining kidney into the rectosigmoid.

There were 292 operations on the prostate gland, with a mortality rate of 6.5 per cent. Failure to recover was due to pyelonephritis in 9 cases, bronchopneumonia in 4 and embolic pneumonia in 3, whereas postoperative hemorrhage, cardiac failure and pulmonary embolism each was the cause of 1 death. In this group of 292 cases prostatectomy was performed for carcinoma of the prostate gland in 11. In 59 cases in which the prostatic obstruction was confined to a median bar or contracted vesical neck, the obstruction was relieved by a transurethral punch operation. Prostatectomy was done for fibroadenomatous hypertrophy in 222 cases. Suprapubic cystostomy was done in 230 cases; in 163 it was preliminary to prostatectomy. In 37 cases cystostomy was done to relieve prostatic obstruction, the result of inoperable carcinoma of the prostate gland. In the remainder of the 230 cases cystostomy was done secondarily for conditions such as vesical and prostatic calculi, cord bladder, periurethral abscesses and fistulas.

Sixty-three operations were performed on 52 patients with carcinoma of the bladder. In 18 of these cases the lesion was removed by segmental resection of the bladder. In 20 cases, after suprapubic exploration of the bladder, the lesion was removed by cautery or electrocoagulation, with insertion of radium at the same time in 7 of these. In 4 cases, cystotomy with insertion of radium was carried out alone. In 1 case already mentioned, successful cystectomy was performed after ureterosigmoidal transplantation. There were 65 cases of vesical tumor in which, because of the size and nature of the tumors, the treatment

was electrocoagulation through the cystoscope. This necessitated a total of 115 treatments. Diverticulectomy was performed in 22 cases with 1 death.

Braasch⁶⁰ stated that the field of cystoscopic manipulation and operation has been considerably developed. Fifty-nine punch operations were done for prostatic disorders with only 1 death. The operations were performed with a direct vision punch instrument, followed by the application of cautery to bleeding vessels to control the hematuria. Obstructing portions of the prostate gland have been removed by means of the punch operation more generally in recent years. Approximately 25 per cent of the patients with prostatic obstruction observed at the Mayo Clinic are treated by this method. The operation is usually employed only if the obstruction is confined to the median lobe of the gland and to contraction of the vesical neck.

Twenty-seven cases of stone in the ureter were reported, in which the stone was removed by cystoscopic manipulation. This does not include a number of cases in which small calculi were passed some time after ureteral catheterization. By various manipulative measures successful removal of stones from the lower part of the ureter has been done in a high proportion of patients observed in the clinic. Many of the stones removed have been of considerable size. Surgical treatment for small stones in the ureterovesical region is seldom necessary. When the stone is situated above the lower third of the ureter it is usually inadvisable to attempt removal by manipulation; it is better to remove it by surgical operation.

A considerable number of tumors of the bladder were treated by cystoscopic or transurethral methods. The selection of tumors amenable to such treatment is largely dependent on biopsy of specimens removed through the cystoscope. Approximately 25 per cent of tumors of the bladder observed were suitable to cystoscopic manipulation.

TUMORS OF THE GENITO-URINARY TRACT

Dean⁶¹ considered the early symptoms and diagnosis of carcinoma of the genito-urinary tract. Adenocarcinoma or hypernephroma, which is the most common malignant tumor of the kidney, is rarely discovered early. Hematuria is the initial symptom in about 85 per cent of the cases, and may or may not be accompanied by pain. Other symptoms include pain in the region of the kidney, tumor, loss of weight and strength and discomfort due to metastasis. Pyelography aids greatly in the diagnosis, since it shows filling defects in most cases as the growth

60. Braasch, W. F.: Discussion, Proc. Staff Meet., Mayo Clinic 6:100 (Feb. 18) 1931.

61. Dean, A. L.: Early Symptoms and Diagnosis of Cancer of the Genito-Urinary Organs, Am. J. Surg. 8:988 (May) 1930.

invades the pelvis. Metastasis occurs most frequently in the lungs, the long bones, especially of the lower extremities, and the bony pelvis.

The usual symptoms of carcinoma of the bladder are hematuria, urinary frequency and dysuria. Cystoscopic examination gives definite and detailed information concerning the condition. Papilloma, papillary carcinoma and flat carcinoma present rather characteristic pictures. Biopsy should be done to determine the type and degree of malignancy, and cystoscopic examination should be supplemented by cystography.

Carcinoma of the prostate gland is not rare and should be considered in the examination of all men of middle age who have urinary symptoms. The onset is insidious, the first symptoms usually being those of obstruction of the bladder. Frequency, difficulty in urination and dysuria are common. Pain low in the back or in the penis, perineum or rectum is usually due to a large congested tumor. Involvement of or pressure on the nerves of the pelvis may cause radiating pains along the thighs. Diagnosis is commonly made by rectal palpation. The prostate gland is usually large, nodular, indurated and fixed. Roentgenograms should be taken of the lumbar portion of the spine, pelvis and femurs in search of metastasis.

Teratoid tumors of the testis usually occur in men aged less than 40 years. The first symptom is a painless swelling of the testes. Palpation discloses a testicular tumor, and examination with transmitted light reveals its solid nature. At the upper limit of the swelling there is usually well defined demarcation. Teratoid tumors are likely to be confused with gumma and tuberculosis. The former usually can be distinguished by a positive Wassermann reaction, and the latter by involvement of the epididymis, prostate gland and seminal vesicles. Abdominal metastatic nodules are deeply situated, rounded, solid and immovable. Metastasis should also be sought in the lungs and mediastinum. If other diagnostic measures are inconclusive, the tumor may be subjected to an erythema dose of high-voltage roentgen rays directed toward the center of the mass. Unless the tumor is composed of radio-resistant adult tissues, rapid regression in size will establish the diagnosis.

The two types of carcinoma of the penis, papillary and flat, originate almost invariably beneath a tight, redundant prepuce or one seldom retracted and cleaned. A foul discharge is present in both types. In a series of 75 cases, the first symptom in 73 per cent was a small sore on the penis. In 9 per cent of the cases increased irritation was followed by the appearance of a small sore; in 5 per cent paraphimosis was present, and in 5 per cent warts beneath a tight prepuce were first noticed. Occasionally the first sign of the disease is a hard nodule in the distal third of the penis. When retraction of the prepuce is impossible, a dorsal slit or lateral incision will be required for examination.

The final diagnosis must be made by histologic examination. Inguinal metastatic nodules may be distinguished from purely inflammatory nodules by greater induration and, in the later stages, by immobility.

Astraldi⁶² reported on the present status of treatment of tumors of the genito-urinary tract in some of the urologic clinics of Paris. In the service of Legueu, nephrectomy for carcinoma of the kidney is performed without resection of fat; enlarged lymph nodes are excised if found. Roentgen treatment is not employed, and radium treatment is considered impracticable. Ureteral papillomatosis is treated by nephrectomy and total resection of the ureter. In cases of malignant growths of the bladder total cystectomy is performed in two stages. The first stage is bilateral ureterostomy, and the second stage is incision of the bladder two months later. In the interval between operations deep roentgen treatment is employed if the general condition of the patient permits. The mortality is 50 per cent due to the poor condition of the patients rather than to shock. Partial cystectomy is performed if tumors are in the dome of the bladder. Electrocoagulation after cystotomy is a simple and safe procedure; the tumors always recur. The application of radium after cystotomy is of no value. Deep roentgen treatment gives relief from pain, urinary frequency and hematuria; unless the patient is resistant to irradiations, profound anemia will result. Mesothorium is employed in cases beyond surgical aid. Because of the results obtained, Legueu recommends mesothorium in every case of neoplasm of the bladder, irrespective of what has been used or is to be used.

In carcinoma of the prostate gland, Legueu does not resort to operation, roentgen rays or radium. Implantation of radium needles is employed in the treatment for penile carcinoma. Partial or total amputation has been abandoned. Lymph nodes are not treated by roentgen rays, but are resected if enlarged.

Chevassu performs nephrectomy for carcinoma of the kidney only if the tumor is small and if the renal pedicle is not invaded. In his series of 22 cases of nephrectomy for renal carcinoma 18 patients are still living about twelve years after operation. In cases of carcinoma of the prostate gland he uses radium.

Papin treats carcinoma of the kidney by nephrectomy with total resection of the perirenal fat and lymph nodes of the hilus. A cure or at least prolongation of life is obtained in 25 per cent of cases. In carcinoma of the renal pelvis and ureters, the kidney, ureter, ureteral meatus and the corresponding half of the trigonum are removed. Metastasis is infrequent, and the results obtained are good. Perineal

62. Astraldi, Alejandro: *Recuerdos Científicos de Viaje*, Rev. de especialid. 5: 742, 1930; abstr. in *Am. J. Cancer* 15:489 (Jan.) 1931.

prostatectomy is done in cases of encapsulated carcinoma of the prostate gland. Tumors that infiltrate beyond the capsule are treated by radium or roentgen rays.

ANURESIS

Eisendrath⁶³ reported 9 cases of anuresis, and stated that there are three types: secretory, obstructive and transitional.

The secretory type includes all cases in which there is a cessation of secretion as the result of disturbance either next to the kidney or within its parenchyma. There are several classifications in this group. Under disturbances of circulation proximal to the kidney itself may be included vascular spasm of the main renal vessels, probably as the result of stimulation of the splanchnic nerves; anuria as a symptom of hysteria; reflex inhibition of secretion as a result of peripheral irritation; embolism or thrombosis of the main renal vessels of both sides or of one side with reflex irritation of the opposite kidney; marked decrease in blood pressure as often seen in shock, and dehydration due to loss of large quantities of fluid. Under disturbances affecting the renal parenchyma may be placed anuresis complicating the various types of nephritis and nephrosis.

The obstructive type includes unilateral block by calculus, stricture, injury or neoplasm, with the opposite kidney normal. Anuresis in such cases is explained by reflex inhibition of the secretory activity of the opposite organ, a combination of obstructive and secretory anuresis. Another variety of the obstructive type is unilateral block by calculus, stricture, injury or neoplasm with the complete loss of function or absence of the opposite kidney. There is also bilateral block by calculus and stricture.

Among the transitional group are cases following transfusion, burns, infection with gas bacillus, poisoning by potassium chlorate and black-water fever from malaria. The obstructive factor is in the form of blocking innumerable renal tubules by hemoglobin crystals and a resultant interference with the secretory activity of the renal parenchyma.

In the treatment for anuresis the type should be ascertained as soon as possible. The prognosis is not usually as favorable in the secretory type. The methods of treatment which may be employed are: 1. Administration of large quantities of fluid by proctoclysis, hypodermoclysis, intravenous administration and by the duodenal tube. 2. Nerve blocking, a comparatively recent method, depending on the ability to block the nerves that inhibit renal secretion. 3. Decapsulation. Several cases in which treatment was successful have been reported. Decapsulation for nephrosis caused by corrosive mercuric chloride has only been followed by one recovery in 23 cases reported.

63. Eisendrath, D. N.: Anuria, *J. Urol.* 25:421 (April) 1931.

4. Ureteral catheterization. This offers the best outlook in cases of obstructive anuresis and should be given a trial for forty-eight hours but not longer. 5. Operative procedures. These depend somewhat on the experience of the individual operator and are employed in cases in which ureteral catheterizations, splanchnic block and other methods have failed; some surgeons prefer nephrostomy, pyelostomy or ureterostomy, respectively, with removal of the calculus at the same time.

CARCINOMA OF THE SINUS TRACT

Watson⁶⁴ stated that continued irritation of urine discharging through sinus tracts from the kidney, ureter, bladder or urethra tends to stimulate hyperplasia, particularly at the epithelial border, and to a lesser extent along the tract itself.

Two cases are reported of primary carcinoma of a suprapubic sinus, each occurring many years after a stricture of the urethra for which suprapubic cystotomy had been performed. One case was of traumatic origin, and the other of gonorrheal. In each case secondary infection had been present for several years. In one case excision, radium and deep roentgen rays were used, but the patient died of generalized carcinoma in three months. In the other case, in which radium implantation and deep roentgen rays were used, the patient lived two years and died of uremia following an operation for hernia. There was no clinical or palpatory evidence of carcinoma.

PYELOVENOUS BACKFLOW

Fuchs⁶⁵ found that in acute stasis and increased pressure of the renal pelvis of a rabbit, there is no back pressure into the tubules, but the urine is forced interstitially into the venous system. With the occurrence of acute stasis and increased renal pressure, this interstitial infiltration soon decreases and finally becomes less than the normal renal pressure. If the acute process becomes chronic, there is a corresponding change in the renal parenchyma. In this process the backflow changes from the venous system to the tubular. These observations are correlated to the problem of formation of early hydronephrosis in which there is a decrease in intrarenal pressure. Thus the preliminary conditions for the development of hydronephrosis are formed. Kidneys, such as those of dogs, which lack these phenomena and in which the lower pressure causes backflow into the tubules, become atrophied.

64. Watson, E. M.: Sinus Tract Carcinoma, *J. Urol.* **25**:469 (May) 1931.

65. Fuchs, Felix: Pyelovenöser Reflux und Hydronephrose: Eine Untersuchung über die Pathogenese der Sacknieren, *Deutsche Ztschr. f. Chir.* **224**:353 (June) 1930.

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